

American Journal of Obstetrics and Gynecology

VOL. 36

NOVEMBER, 1938

No. 5

American Gynecological Society

Sixty-Third Annual Meeting, May 30 to June 1, 1938

Dr. N. Sproat Heaney, Presiding

PRESIDENTIAL ADDRESS*

N. SPROAT HEANEY, M.D., CHICAGO, ILL.

AT THIS time, when considerable thought is being devoted by the medical profession to the licensing of specialists in the various branches of medicine, it may not be considered amiss for the President of the American Gynecological Society to express a few thoughts relative to the training of specialists in obstetrics and gynecology.

Now that formulas for preliminary training are being outlined and published, it becomes apparent from the large number of applications for residencies being received everywhere, that great care must be taken if sufficient suitable positions are to be supplied. At the present time, chiefly in the larger cities and particularly in connection with medical schools, there are a large number of hospitals which accept interns for their fifth year's work where the practice of the hospital is so specialized or the rotation of the internship is so restricted that the intern does not get a good general training. The medical colleges should be stricter in their certification of hospitals for the required or fifth year, and should exact that the internship should be widely rotating and general to the extreme in the nature of the training given. Six months' service in internal medicine and six months in general surgery is quite commonly accepted as a substitute for the required internship. This would not seem comprehensive enough for entering general practice in which so much of the practitioner's work has to do with obstetrics and the attention of sick children, nor is it a broad enough experience to use as the base upon which to build a training in some specialty. When,

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

furthermore, the service in internal medicine may be limited to metabolic diseases and the surgical experience may be largely limited to abdominal work, the training the intern receives lacks much of what should be expected of the fifth year. It may be possible for an intern to get a better training on a rotating service in a less famous hospital in which the work is more general and less highly specialized. When the work offered an intern by any hospital is not general enough, the medical colleges should remove such an institution from their lists of hospitals approved for the fifth or required year of internship. There are plenty of hospitals with high standards of efficiency in which the nature of the work done is general enough to give interns a broad and varied training for their fifth year, and only such institutions should be approved for this work.

Special hospitals, teaching hospitals, and such institutions where the nature of the patient body or the reputations of the various staff members are such as to make for high degrees of specialization become available at once for the training of specialists, by replacement of the fifth year internships with special internships and residencies. You are looking for methods of measurement to determine goals of achievement and are confronted by the fact that your measuring stick must be flexible instead of rigid and unyielding. There is no inflexible standard for measuring professional ability. In your own acquaintanceships you know self-made men who excel the products of long training, yet since it is well known that training is generally requisite for competency, a minimum standard seems advisable. The length of residency in an institution required for certification would vary with the opportunities offered, but in my mind should not be longer than three years. This length of time skillfully directed should amply train an aspirant in every phase of his specialty and prepare him for a start in the practice of his art. To remain too long in one institution is a real danger for a young man. It is too likely to fix his ideas and limit his development. Too long a period of training in one institution produces the man anxious to tell of his institution's methods of treatment instead of the eager seeker after new methods for his own improvement. This residency period should be broad in its experience and active to the extreme. There is more than wishing to acquiring proficiency. Contemplation does not develop diagnostic acumen, nor philosophic discussion surgical technique. Clinical material should be abundant and responsibility for its management developed. Thorough training in the anatomy and pathology of the specialty is of prime importance. Though a man expects to be an obstetrician he should during these years have enough training in gynecology so that he may be a safe operator in obstetrics when the occasion arises, since indicated obstetric operations do not occur with frequency enough to keep his surgical technique fit. Also now that services in obstetrics and gynecology are being more commonly combined he should prepare himself for that possible contingency in his own future and have a good basic training in gynecology. Equally so should the aspirant in gynecology have, during these hospital years, a good training in ob-

stetries. Certainly the gynecologist should know the physiology of the genitalia, which is childbearing, and studying obstetrics is essential to his training. The stamp of the obstetrician is seen in the character of every gynecologist's work who has been trained in both branches. Furthermore, in practice the ability to do obstetrics will enable the novice quickly to establish his competence, for obstetrics comes easily to a young man while gynecology is coy and demands more evidence of age. Thus a young gynecologist may early practice his specialty and not make excursions into the general surgical field in which he is untrained in order to earn a livelihood, nor slump into general practice for which he is equally unsuited. Finally in his degenerative years the man thus trained may leave his obstetrics to physically able young men and avert untimely death by retiring to gynecology, where he may be active and efficient with a minimum of effort, not only to his own benefit but that of the obstetric and gynecologic cases which demand his attention.

After three years, sometimes sooner, he should leave the hospital of his special training and seek some other connection. Nothing is so illuminating as a change of chiefs. The next year he might well spend in travel and in taking special courses to make up the deficiencies in his training. There can be no question of the great benefit many of us obtained from our years in Berlin, Dublin, London, Edinburgh, or Vienna, years ago before war and near war made these centers difficult for study. We returned with new ideas, new ambitions, and new ideals. The effect of this training on American obstetrics and gynecology is still felt today. Now that such traveling is impractical and unsatisfactory for many reasons, we should encourage young specialists to travel more among the American clinics which are the equal of any abroad. In one center he would find much to stimulate him in investigation, in another he would find an entirely new attitude toward clinical problems which had been satisfactorily settled as far as his previous training had led him to believe. We should not be so satisfied with our own methods and our own technique that we do not encourage our young men to visit others where possibly better approaches to the attack on disease may be employed. An impressive teacher may so imbue a student with his beliefs and methods that the student feels no urge to seek further fields for truth, and inbreeding results. There seems something innate in the active surgical teacher which gives the impression that all truth rests in him. It might not be advisable to disabuse the minds of patients, nurses, and secretaries regarding the fallacy of this created opinion, but we really owe it to our own assistants to rob them of this delusion, so that they in turn may not be bound by our own limitations. They should visit other centers, seek knowledge elsewhere, and thereby lessen the chances of their not excelling their chiefs. Many of us in charge of large clinics have discarded every operative procedure which we once employed and have established new technique, based upon ideas picked up here and there while visiting elsewhere.

Or this fourth year might be spent in a laboratory of investigation where research work is done. There is a move on foot to require research work of every candidate for specialization. This is laudable if practicable. Progress in medicine can only be expected through investigation. The man with a research type of mind can best evaluate the clinical application of new discoveries, but shall we require this as a necessary qualification for licensure? If so, where will all these candidates find qualified masters to teach them, or can a few teachers be expected to turn to mass production? What constitutes research work in Gynecology and Obstetrics? In History it consists in seeking the original historical data in archives and libraries. In English an investigator may gain repute by his discovery of new unpublished bits from Chaucer. In our specialty much acclaim is given him who works in physiology, chemistry, or physics. Once reputations were firmly established by researches into the morphology of tissues. Not much credit is given to the student of histology today as being engaged in research work, yet I must draw to your attention that in my opinion the painstaking studies of Sampson, resulting in our knowledge of the nature and behavior of endometriosis, has had far more effect on the practice of gynecology today than any other single bit of research work done during the same period in obstetrics and gynecology, whether test tube and guinea pig were used or not. So before research or investigation is required real research and investigation must be defined. One thing which should not be lost sight of is that the various boards of licensure are trying to establish indices for the fitness of candidates to practice their specialties; in our specialty, for example, whether they are competent to be declared "Approved for the practice of gynecology and obstetrics." What has that to do with research work? This board is not qualifying men for heads of departments in medical colleges. You cannot hope to regulate the production of leaders. Leaders cannot be kept down, they will develop in spite of regulation. You can hope only to develop good followers of which there are not enough. At present I believe that a great deal of self-deception exists among us as to the real value of the research work we engage in, both as to its value to us as individuals and the progress of medicine at large. He who has research ability is fortunate, and this ability should be fostered and encouraged and I may say steadied and not allowed to go off half-cocked to be corrected in a subsequent arbeit. In his fourth year a young specialist should be full of problems demanding solution, if he has a research mind, and a year under a recognized investigator in a physiological, chemical, or physical laboratory will teach him exact methods. The proper teacher will help him with problems concerning his specialty, and if he is a good teacher he will determine whether the aspirant has the mind to prosecute research work or should end his self-deception. At any rate research work must not be a fetish and should be an addition to adequate clinical and technical training. It should not, by any stretch of the imagination, be considered a substitute.

After the third hospital year, the aspirant may be taken into a specialist's office as an assistant for further training. This is not only

helpful to the chief but can be made of the greatest value in the training of the younger man. In the hospital the resident has seen chiefly the seriously sick, or at least those requiring hospitalization. In an office or dispensary practice he sees, in addition, the beginnings of disease and finds that many applicants for medical relief need only the assurance that nothing ails them to obtain that relief. An assistant should be chosen not because he is affable and likable but because he will make an able successor. That he may too soon become a successor is the fear which closes this valuable avenue of training to many. Nothing is so horrendous in its results as selecting assistants because they are good "yes men." How often the mantle of succession to a professorship has been placed on the shoulders of such a "yes man" grown older, to the detriment of the progress of medicine.

Years ago I became aware of the fact that if I were to train teachers for my staff at the college and hospital I would have to do it through accepting assistants in my office, for the teaching and clinical beds at my disposal were too few to train adequately the men under me in a reasonable time. I remodeled my office so that a large number of patients could be attended. Fixed fees were abandoned and all who wished attention were made welcome. As largely as possible the active care of patient was turned over to the ministrations of my assistants and my own attention was given to the supervision of their work and the treatment of the most exacting or complicated cases. Obstetric and gynecologic cases were handled alike and the fees of the poor and of persons with limited means were largely a matter of their own decision. The rich came along with the poor, were charged abundantly, and were happy in most instances to pay the fees exacted, because they had before them the visible reasons for variations in fees. Assistants were taken on for a period of three years. In order that the assistants' activities could be controlled and their time best occupied for their own learning and advancement, flat salaries were paid for the disposition of all their time and efforts, and the salaries were increased for each year of service. The salaries were sufficiently ample that at the end of three years the assistant could pay for a year's study abroad. When this calculation failed I loaned them enough money to make up the deficiency. In this way I built up a large practice to the satisfaction of all concerned, and today I have the records of over 11,000 admissions to my office. When it is taken into consideration that for the first several years the work was largely obstetric and that many of these patients had several children, the amount of work done was considerable. When it is further stated that this does not include dispensary activities pursued at the same time, nor clinical patients or those seen only at the hospital, nor consultations on other services in our own hospital or other hospitals, except when occasionally the patient would return to the office, it becomes apparent that our experience was a rich one. After returning from his foreign training the assistant goes into private practice on his own responsibility. He is allowed to notify such of my clientele as were earlier turned over to him for his attention that he is

in practice for himself, is given a position on the staff of the hospital and on the teaching staff of the medical college. Each of these graduates from my office is assured of a private practice in his specialty out of my own clientele, but this pruning has never injured the parent practice which has endured both the depression and so far the recession. In this way one may make up the deficiencies of insufficient institutional positions both to the progress of obstetrics and gynecology and to one's own satisfaction.

Surgery is defined as that branch of the healing art which resorts to manual operations or mechanical appliances for the treatment of injuries, deformities, or morbid conditions. Surgery is an art and dexterity and proficiency in it come only through much training and hard application, and for the acquisition of this art there can be no substitute for a large experience. Artists and musicians are content to spend long hours daily in gruelling training in order to obtain manual dexterity and supple action. Acrobats and prestidigitators perform the same act daily for hours to train the muscle sense in order that they may do their particular stunts with the most exacting precision. The tap dancer and knife tosser perform their feats, not through a gift bestowed upon them, but accomplish the acts which astound us only after months and years of exacting training. These artists stake their reputations and often their lives on their sheer ability. They strive to excel in their respective arts and their only hope is to amuse us and thereby earn their competence. We deal in human lives. Quick judgment may be based on temperament but its chief support is experience—without experience there is no basis for judgment. Operative dexterity is an asset best appreciated when dealing with the poor operative risk. Many people die from operations who might live were the operator a little more skillful, a little more experienced. These facts cannot be denied. Why, then, are we so casual about our skill, so inclined to disparage technique and why do we try to substitute something else for this indispensable attainment?

In the last analysis examinations for licensure have not as yet been devised which will indicate a candidate's real ability, whether he is an obstetrician and gynecologist of judgment and experience. Were he able to demonstrate that fact he has passed beyond the need of licensure, he has arrived.

ELECTRICAL CHANGES ASSOCIATED WITH HUMAN OVULATION*

JOHN ROCK, M.D., JEAN REBOUL, M.D., AND JAMES M. SNODGRASS, A.B.,
BOSTON, MASS.

(From the Fertility Clinic, Free Hospital for Women, and the Department of Physiology, Harvard Medical School)

STUDIES of mammalian ova (Pincus;¹ Allen, Pratt, Newell and Bland;² Young and Blandau³) justify the conclusion that, like other cells of the body, the mature fertilizable ovum is dynamic, and when it has reached its limit of autogenous growth, it must be fertilized within a short time or perish. The exact limit of this "short time" has not been determined, but by analogy to data obtained particularly on the rabbit (Pincus)¹ and on the monkey (Hartman),⁴ we believe that it is of the order of hours and not days. Spermatozoa, too, seem to have but a short functional span, limited perhaps not only by length of life, but by their dissemination. Though one spermatozoon may fertilize, the assistance of many is normally essential. Knowledge then of just which hours during any given ovarian cycle the ovum is free and susceptible to spermatozoa, would be of profound value to the rational control of human fertility. Various statistical studies correlating menstruation with coitus and fertility have confirmed the conclusion drawn from endocrine and anatomic studies that ovulation normally occurs in a strictly limited time relation to a subsequent menstruation. This much is exceedingly helpful, but the duration of ovulation time thus indicated is still a matter of four or five days, during only a few hours of which the ovum is actually susceptible to fertilization; and still more unsatisfactory is the fact that the date of the subsequent menstruation from which we may estimate ovulation time is predictable only within a wide range of several days or even weeks.

This report presents experiments designed to determine more directly the exact moment when the mature human ovum is liberated from the follicle.

REVIEW OF LITERATURE

In rabbits, Burr, Hill, and Allen⁵ (1935) detected by means of a vacuum tube potentiometer a marked difference of potential between a suprapubic and a vaginal electrode when each ovulation occurred. Reboul, Friedgood, and Davis⁶ (1937), employing a similar technique, with the abdomen open and the ovaries under inspection, found that the peak of the potential difference was reached at about the moment of follicle rupture. Usually the potential difference passed through a maximum of 6 to 10 mv. within thirty seconds and returned gradually to its former

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

This investigation was aided in part by the Permanent Charity Fund of the Harvard Medical School, by the National Committee on Maternal Health, and by a special grant from the American Academy of Arts and Sciences.

level in five to twenty-five minutes. Furthermore, with electrodes similarly placed, they were unable to obtain anything resembling this type of potential change by dropping follicular fluid into the peritoneal cavity, by injuring the ovarian cortex, or by puncture of other abdominal organs. However artificial rupture of a follicle accomplished without injury to the ovary produced an increase in potential difference like that observed with normal ovulation. In 1937, Burr, Musselman, Barton, and Kelly,⁷ applying electrodes in the same places, obtained marked changes in potential in a human female at the time when, as shown by subsequent laparotomy, ovulation could have occurred. Rock, Reboul, and Wiggers⁸ also reported one similar experiment. In both of these experiments during a period of several hours preceding the moment of greatest potential difference, suggesting by analogy the moment of follicular rupture, there was recorded a slow increase of potential which warned of the approaching event. Substantiation of these two phenomena, a maturation sign and a rupture sign, would have great practical significance.

In a series of experiments on normal, ovariectomized and hypophysectomized rats, Rogers⁹ recorded an increase of potential caused not by changes in the ovary or in the vagina, but by the more generalized phenomenon called *estrus*, and showed that the acme of this potential difference is reached just before the animal passes out of estrus. This electrical disturbance occurs not within five to twenty-five minutes, like the one observed in the rabbit, but the complete rise and fall of the potential takes about fifteen hours.

INDICATIONS OF OVULATION

A major difficulty and fearsome hazard in interpreting the curves of potential changes obtained in human experiments comes from our lack of any other reliable sign of ovulation to which we might refer the observed change in potential. An unpublished study of some 600 human vaginal smears in 1935 taught us that ovulation could not be accurately detected in this way. Rubenstein's discovery of a temperature drop during the hours of follicular maturation and rupture has only recently come to our notice.¹⁰ "Mittelschmerz" we depended on in one allegedly infallible patient and found it of unjustly exaggerated repute. Our resources have not permitted the arduous and time-consuming work incident to continuous hormonal studies.

We planned our experiments therefore to utilize women who needed laparotomy for a condition which did not entail any significant ovarian pathology or dysfunction, and to make our observations between the seventeenth and eleventh days (inclusive) before any likely subsequent menstruation. These dates were computed on the basis of the recent catamenial history. Excluding the controls, and with the exception of one ovulating case, all the women on whom dependable readings were obtained were subjected to laparotomy soon after suggestive changes in potential were recognized, and the condition of their ovaries or ova was used to estimate the time of ovulation. While this means of dating ovulation from the gross or even microscopic findings in the corpus luteum, or from the condition of ova, is inaccurate to an appreciable degree, we believe it to be the most satisfactory method at present.

In six patients examination of the ovaries was made within thirty hours and in one case fifty-one hours after the electrical change. In another patient the curve of ovulation was not recognized until more

than eight days had elapsed.* Operation then showed endometrial and corpus luteum development which, according to present standards, placed ovulation about eight days before operation. One patient was not operated upon but menstruated on the fifteenth day following the observed increase in potential. Such a time relationship between ovulation and menstruation has the sanction of current theory.

TECHNIQUE

Electrodes.—Our methods of electrode contact with two points arbitrarily chosen in the possible field of electrical disturbance, as well as our method of recording differences in the potentials of these two points, have been modified in several ways since the original report.

In our earlier experiments the electrodes consisted of wicks wet with normal saline solution and connected by salt-bridges to silver-silver chloride electrodes which in turn were connected by insulated cables to the vacuum-tube potentiometer. As the contact wicks or the salt-bridges dried too easily we later used a jelly made with agar-agar and normal salt solution into which the silver-silver chloride electrodes were imbedded (Rock, Reboul, and Wiggers⁸). At the present time we use electrodes made by filling a porous rubber cup with salt-agar jelly to which is added a little glycerin to prevent drying. Imbedded in this jelly is a small zinc plate which is connected directly to the recorder. The rubber cups are inverted and firmly applied to the patient's skin by means of paste washed off by xylol from ordinary adhesive tape.

Recording Apparatus.—For measurement of potential changes we first used a vacuum tube potentiometer similar to that of Burr, Lane, and Nims,¹¹ and later a different type which has been described by Reboul, Davis, and Friedgood.⁶ The changes of potential thus detected were recorded by means of a galvanometer and a slow moving camera. Later when it was discovered that the differences of potential were of such magnitude as to permit of a less delicate mechanism, we used an ordinary battery operated slide-wire potentiometer to balance the differences of potential. The slide-wire used was identical to that contained in the Leeds and Northrup Type K potentiometer. At intervals of from five to fifteen minutes we made readings of the voltage necessary to bring a sensitive galvanometer to its zero position. These readings were independent of the external resistance to a sufficient extent.

Since this method proved satisfactory we then used a Leeds and Northrup multi-point recording potentiometer (Micromax recorder). This works on the potentiometer principle, and also provides an automatic record for 6 different circuits every twelve minutes; or, if all leads are used in one circuit, every two minutes. Hence, records may be taken simultaneously on several patients or from different pairs of electrodes on the same patient. In the later experiments we were thus able to use two pairs of electrodes; one pair low in the pelvis, and one pair higher up, and a third circuit recording the difference of potential between the two right electrodes of these two pairs. Three of the 6 circuits provided by the recorder were thus used, and a record obtained from each of these every six minutes. On this apparatus the control experiments were made (with the exception of Experiment 1 on Mr. A. U. where the manually operated potentiometer was employed).

EXPERIMENTAL

Following are the details of nine experiments made on women with normally functioning ovaries during their estimated ovulation time. As controls for the above, observations are presented on three healthy

*Until one is able to determine the magnitude of base line oscillations, it is impossible to recognize the characteristic ovulation curve. (See under experimental results, I, a, page 741.)

young males, two women past the menopause, and one woman in the nonovulatory phase of her cycle.

CASE 1.—Mrs. J. C., aged 34, had had 7 pregnancies.

Diagnosis: Dysmenorrhea. Prolapse. *Pelvic Examination:* Slight vaginal relaxation. Lacerated, eroded cervix. Fundus normal size, forward, freely movable. Vaults negative. *Range of Cycle Lengths:* 26 to 30 days. *Last Menstrual Period:* September 7. *Estimated Ovulation Time:* September 17 through September 25.

Procedure: On September 17 at 2:15 P.M. the salt-bridge electrodes were attached; one was inserted in the vagina, and one placed on the abdomen; the latter served as reference electrode. The vacuum tube potentiometer was employed, and readings of potential changes were taken at five- or six-minute intervals from the deflections of a galvanometer connected to the vacuum tube potentiometer. The experiment ended at 9 A.M. on September 19.

Description of Curve: Due to an error in recording, the data obtained previous to September 18 had to be discarded. On September 18 the record showed a base-line that remained steady within ± 2 mv., until at 9:45 P.M. the potential, then at about 1 mv., suddenly rose, and by the end of two hours (11:46 P.M.) it had attained a peak of nearly 10 mv. (i.e., an increase which was about five times the maximum of the oscillations on the base line).^{*} Then for about three-fourths of an hour the potential remained at a fairly high level. At the end of this period (12:24 A.M.), it dropped suddenly to the original base line level. Unfortunately polarity was not determined here. The peak of the change thus occurred on the twelfth day of Mrs. C.'s cycle.

Operative Findings: Operation at 11 A.M. on September 19 (i.e., twelve hours after the peak had been reached) revealed a freshly ruptured follicle in the right ovary with early corpus luteum formation. This was photographed before fixation. No ovum was recovered from the tubes which were irrigated in situ. Microscopic examination of the corpus luteum showed an open stigma; theca about 24 cells deep; granulosa layer absent; extravasation of red blood cells in small masses among thecal cells.

The endometrium was in the late proliferative stage.

CASE 2.—Mrs. A. F., aged 24, had had 2 pregnancies and 2 abortions.

Diagnosis: Lacerated perineum. Cystocele. Prolapsus uteri. *Range of Cycle Lengths:* 28 days. *Last Menstrual Period:* September 28. *Estimated Ovulation Time:* October 10 through October 14.

Procedure: On October 9 (2 P.M.) the electrodes were applied. A glass-covered vaginal (saline-AgCl-Ag) and a glass-covered abdominal (saline-AgCl-Ag) electrode were used here, the abdominal serving as reference electrode. At noon on October 10 a new abdominal electrode covered by a rubber cup was attached. Voltage changes were usually measured potentiometrically at fifteen-minute intervals.

Description of Curve: For about twenty-four hours the vaginal electrode was slightly negative to the reference electrode; the base line showed oscillations as high as ± 5 mv.

On October 10 (2 P.M.), the vaginal electrode became positive to the reference electrode. The potential increased steadily until at the end of six hours it had attained a peak value of +30 mv. Then in the next twelve hours the potential decreased slowly until it reached a level of +10 mv. At about this time the record was stopped (October 11, 10 A.M.). The peak thus occurred at 8 P.M. on October 10; i.e., on the thirteenth day of her cycle.

Operative Findings: At operation on October 11 at 11:30 A.M. (about sixteen hours after the peak had been attained) a recently ruptured follicle with open stigma was discovered in the right ovary. Microscopic examination revealed the following: The luteinized thecal layer was 12-20 cells deep and contained many vacuoles and

^{*}In this first experiment there is some doubt as to the correctness of the absolute values indicated, as the calibration of the apparatus was doubtful. The relative values are as given in the text.

clumps of extravasated erythrocytes. The coagulum, which also contained many free red cells, lay in contact with the thecal layer. There was no granulosa or limiting membrane.

CASE 3.—Mrs. H. D., aged 37, had had 2 pregnancies.

Diagnosis: Lacerated perineum with cystocele and prolapsus uteri. *Range of Cycle Lengths:* 26 to 32 days. *Last Menstrual Period:* October 12. *Estimated Ovulation Time:* October 22 through November 1.

Procedure: On October 23 (1 P.M.) one pair of surface electrodes (saline-agar-zinc plate) and one pair of vaginal-abdominal electrodes (saline-AgCl-Ag) were applied. Potentiometric determinations of the voltage were recorded at seven- and eight-minute intervals alternately; i.e., a reading was obtained for each circuit every fifteen minutes. The experiment ended on November 1 (8 A.M.).

Description of Curve: On October 23 (5 P.M.) the right surface electrode showed a steady increase in the positive direction with respect to the left electrode until at the end of four hours it had attained a peak value (9 P.M.). The total increase amounted to about 24 mv. Then began a rapid decrease of potential during two hours followed by moderate fluctuations for about ten hours after which it returned to the initial value. (This change in the surface curve closely resembles the curves obtained in Cases 1 and 2.) Throughout the rest of the experiment the base line remained steady within ± 5 mv. and no other characteristic changes were observed. The peak thus occurred on the twelfth day of her cycle.

On the abdominal-vaginal circuit the base line remained constant (within ± 5 mv.) and no typical fluctuations were noted.

Operative Findings: Laparotomy performed at 12 Noon on November 1 (i.e., eight days and fifteen hours after the peak had been reached) revealed the presence of an old corpus luteum in the left ovary. On section this proved to consist of solid cellular folds. The coagulum appeared to be undergoing fibrosis.

The endometrium was in a well-advanced secretory stage. In the convoluted and saw-toothed glands the epithelium was characteristic of the beginning of the final week of the cycle. The nuclei were basal, and the supranuclear cytoplasm was vacuolated and fragmented. The stroma was moderately edematous except in those areas where the cells were enlarged by a marked increase of cytoplasm. A cellular picture of this type has already been shown to be characteristic of progestin influence over a period of about nine days.¹² The corpus luteum, too, as noted above, was mature. The curve described was obtained on the ninth day preceding operation.

CASE 4.—Miss T. C., aged 21.

Complaint: Dysmenorrhea. *Pelvic Examination:* Nulliparous vagina. Cervix, not lacerated or everted, pointed directly anterior. Fundus of normal size; ante-flexed and deeply retrocessed. Vaults negative. *Diagnosis:* Essential dysmenorrhea. *Range of Cycle Lengths:* 25 to 30 days. *Last Menstrual Period:* October 29. *Estimated Ovulation Time:* November 7 through November 16.

Procedure: On November 8 (2 P.M.) the electrodes were attached. These consisted of one pair of surface electrodes (agar-saline-zinc plate) placed low in the groins, the reference electrode being on the left side. Voltage changes were read by the null potentiometric method at fifteen-minute intervals.

Description of Curve: For the first seven days there was no significant change. During the early half of the week, however, the curve showed slow cyclic oscillations of period one day and of amplitude about 16 mv. On November 15 at around 12 midnight there was a sudden rise from the base line to a value above +80 mv.* The potential remained at this level for about five minutes. It then dropped within an hour to +24 mv. where it stayed constant for six hours. Soon afterward the record was stopped (10 A.M., November 16). The peak here occurred on the eighteenth day of the cycle.

Operative Findings: At operation on November 16 (12 Noon), twelve hours after the peak had been reached, there were recovered from the right ovary a young corpus luteum and one well-developed follicle, and from the left ovary one large follicle and

*Eighty millivolts are the limit of the potentiometer scale.

several adjacent ones. The ovum obtained from the follicle in the right ovary, as well as two of the ova recovered from the left ovary, were not sufficiently atretic to be unattractive to spermatozoa.

Microscopic examination revealed a young corpus luteum, the theca interna of which had a depth of 10 to 20 cells. Among these, extravasated blood cells appeared in many small spaces as yet unlined by endothelium. However in the outer layer of this luteinized theca centripetal capillaries were apparent. The granulosa layer was absent. The immaturity of the corpus luteum, as well as the absence of degenerative changes in the ova of other follicles, implied, we believe, that ovulation had occurred not more than twenty-four hours before operation.

The endometrium was in the early secretory stage.

CASE 5.—Mrs. M. G., aged 27, had had no pregnancies.

Complaint: Sterility. *Diagnosis:* Bilateral tubal occlusion. *Pelvic Examination:* Normal introitus and vagina. Cervix of normal size, shape and position; movable. Fundus of normal size, anterior, movable. Slight thickening in left vault. Right vault negative. Very slight first degree prolapse. Mucoid cervical discharge. *Range of Cycle Lengths:* 27 to 29 days. *Last Menstrual Period:* October 5. *Estimated Ovulation Time:* October 16 through October 22.

Procedure: On the morning of October 16 a rubber-covered electrode (saline-AgCl-Ag) was applied on the abdomen, and a glass-covered electrode (saline-AgCl-Ag) was inserted in the vagina, the abdominal serving as reference electrode. The first reading was taken at 11:05 A.M. and subsequent readings usually at fifteen-minute intervals. The experiment ended at 5:30 P.M. on October 19.

Description of Curve: This curve is characterized by a very rapid potential increase of 24 mv. in the negative direction beginning on October 18 at 5:30 A.M. The potential remained high for about eight hours after which it gradually returned in nineteen hours to the original base line which previously had shown oscillations not greater than ± 5 mv. The peak here thus took place on the fourteenth day of the cycle.

Operative Findings: Operation at 10 A.M. on October 20 (fifty-one hours after the peak had been attained) disclosed in the right ovary one freshly ruptured follicle with open stigma. Microscopic examination showed a luteal layer about 20 cells deep which was vacuolated and infiltrated with extravasated blood. Many dislodged granulosa or theca-lutein cells were free in the coagulum.

The endometrium was in the late proliferative phase.

CASE 6.—Mrs. H. G., aged 27, had had no pregnancies.

Complaint: Sterility. *Pelvic Examination:* Normal except for hypersecretion of cervical fluid. *Range of Cycle Lengths:* 25 to 31 days. *Last Menstrual Period:* November 5. *Estimated Ovulation Time:* November 14 through November 24.

Procedure: On November 15 (12 Noon) 2 pairs of surface electrodes (saline-agar-zinc plate) were applied. The left electrodes served as reference electrodes in both pairs. Manual potentiometric determinations of voltage were recorded at five- and ten-minute intervals alternately; i.e., a reading was obtained for each circuit every fifteen minutes. The experiment ended at 4 P.M. on November 17.

Description of Curve: Between 3 and 4 P.M. on November 15 (i.e., within one hour) the right lower electrode became about 40 mv. more positive with respect to the left electrode, and then returned very slowly to its original potential in about thirty-six hours.

This change was not reflected on the upper pair which showed a base line steady within ± 6 mv. and shifting slowly from a zero position to a slight positivity.

This patient was not operated upon, but she did start to menstruate on November 30, the fifteenth day after the peak was reached. This menstrual period occurred on the twenty-sixth day of her cycle. The peak had been observed on the tenth day.

In the following three experiments potential changes very similar to those described above were obtained yet ovulation had not occurred.

CASE 7.—Mrs. H. C., aged 37, had had 4 pregnancies and 1 abortion.

Diagnosis: Rectocele. Cystocele. Prolapsus uteri. *Range of Cycle Lengths:* 28 to 30 days. *Last Menstrual Period:* November 1. *Estimated Ovulation Time:* November 12 through November 18.

Procedure: On November 13 (11 A.M.) the electrodes were attached. These consisted of one pair of surface electrodes, placed low in the groins (saline-agar-zinc plate), the reference electrode being on the left; and one pair of glass-covered vaginal-abdominal electrodes of the salt-bridge type referred to previously, the abdominal serving as reference electrode. Manual potentiometric determinations of voltage were recorded alternately at five- and ten-minute intervals; a reading was thus obtained for each circuit every fifteen minutes. The experiment ended on November 14 at 9 A.M.

Description of Curve: On November 13, two hours after the experiment was started, there was a sudden change in potential difference from +10 mv. at 1 P.M. to -24 mv. at 4 P.M. under the right surface electrode. Near this level it remained for about twelve hours. The potential difference then gradually diminished to -10 mv. At this time the record was stopped.

The vaginal electrode, which was slightly positive (5 mv.) at 1 P.M. (November 13), became slightly negative by about 10 mv. during the next two hours and then slowly returned to a positive level of +12 mv. where it remained steady for a period of ten hours. The peak of negativity was synchronous with the maximum change over the right surface electrode, which, as mentioned above, was one of 34 mv. in the negative direction. The peak here occurred on the thirteenth day of the cycle.

Operative Findings: At operation on November 14 (11 A.M.), nineteen hours after the peak had been reached, one mature *unruptured* follicle was recovered from the left ovary and this contained an egg which in vitro vigorously attracted spermatozoa. On microscopic examination the wall of this follicle showed a fair degree of luteinization of the theca interna. The behavior of the ovum and the condition of the follicle wall strongly suggested that ovulation was imminent.

The endometrium was in the late proliferative stage.

CASE 8.—Mrs. M. M., aged 21, had had no pregnancies.

Complaint: Sterility. *Dysmenorrhea.* *Diagnosis:* Pelvic inflammatory disease. Adherent retroversion. *Range of Cycle Lengths:* 28 to 30 days. *Last Menstrual Period:* November 7. *Estimated Ovulation Time:* November 19 through November 25.

Procedure: This patient was tested from November 16 (11 P.M.) to November 19 (5 A.M.). Two pairs of salt-agar-zinc surface electrodes were used; one pair just above the symphysis and one about 2 inches higher. Manual potentiometric determinations of voltage were recorded alternately at five- and fifteen-minute intervals; i.e., a reading was obtained from each circuit every twenty minutes.

Description of Curve: The potentials recorded by the upper pair remained fairly steady throughout the entire experiment. The difference in potentials recorded by the two lower electrodes remained fairly constant during only the first thirty-six hours. At 1 P.M. on November 18 the right lower electrode suddenly became more negative to the left (reference electrode) by 60 mv. The peak was observed at about 2 P.M., the complete rise and fall of the potential occurring within two hours. This was followed by a period of relative steadiness for twelve hours, although the right electrode became slightly positive to the left electrode, as contrasted with its initial slight negativity. Following this there was noted at 2 A.M. on November 19 a second rise of 40 mv. in the same direction as the first increase. It is interesting that, with the single exception of a sudden rise in Miss T. C.'s record (Case 4), we did not obtain this kind of swing in any of the patients who did ovulate during the experiment. The peak occurred here on the twelfth day of the cycle.

Operative Findings: On November 19 (11 A.M.) twenty-one hours after the peak had been attained, laparotomy was performed. The left ovary measured 2 cm. in diameter and contained a follicle which protruded through the ovarian cortex over an area measuring 2 mm. in diameter. The right ovary measured 3 by 2½ by 3 cm. and was filled with many follicles. One of these was about 1 cm. in diameter and had a very thin wall over an area of 4 mm. None of the follicles had been ruptured. Unfortunately the section containing the largest follicle from the right ovary was lost. Prior gross examination, however, indicated its maturity.

The endometrium was in the late proliferative stage.

CASE 9.—Mrs. C. W., aged 33, had had one pregnancy.

Diagnosis: Inguinal hernia. Retroversion. Ovarian cyst. *Range of Cycle Lengths:* 25 to 28 days. *Last Menstrual Period:* September 29. *Estimated Ovulation Time:* October 8 through October 15.

Procedure: This patient was tested from 12 noon on October 6 through 7:15 A.M. on October 9. The electrodes were similar to those used in Case 5; i.e., a rubber-covered saline-AgCl-Ag electrode was applied to the abdomen (reference electrode), and a glass-covered saline-AgCl-Ag electrode was inserted into the vagina. Readings were taken usually at fifteen-minute intervals.

Description of Curve: No base line was obtained for the first twenty-four hours, but a continuous drift occurred; i.e., the electrode which was 20 mv. negative to the reference electrode became 12 mv. positive. Then for the next twelve hours the record was relatively flat with changes in base line no greater than ± 5 mv. At 1 A.M. on October 8 the vaginal electrode became strongly negative to the reference electrode, a change of 25 mv. which took place in about three hours. After this followed a period of great irregularity (oscillations of ± 10 mv.) which might have been due to defects of technique or electrode difficulties. The curve then returned to the first positive level which it attained twenty-four hours after the beginning of the change. The peak thus occurred at 4:30 A.M. on October 8, the tenth day of the cycle.

Operative Findings: At operation on October 9 at 10:30 A.M. (thirty hours following the peak of the curve), a mature follicle which had recently suffered atresia was found in the right ovary. Microscopic examination of this follicle revealed the presence of a well-developed granulosa layer in which beginning degeneration was evidenced by diminution in the size of the marginal cells and their increased affinity for stain. From this follicle was obtained a slightly elliptical ovum which was surrounded by granulosa cells and was *not* attractive to spermatozoa.

To summarize then: in ten satisfactory experiments (one reported in a previous paper⁸) similar potential changes were observed. Seven of these were associated with ovulation; three of them were associated with maturation of follicles, which, however, had not ruptured.

CONTROLS

In the six control experiments outlined below, the following subjects were tested: (A) 3 healthy young males (control Cases 1, 2, and 3); and (B) 2 women past the menopause (control Cases 4 and 6), and one woman in the nonovulating phase of her cycle (control Case 5).

In all control experiments two pairs of surface electrodes (saline-agar-zinc plate) were used, one pair being placed just above the symphysis, and one pair just below the umbilicus. In the first experiment on control Case 1 (Mr. A. U.) the manual potentiometric method of measuring potentials was employed. In all subsequent control experiments the Micromax recorder was used.

A. Male Controls.—CONTROL CASE 1.—Mr. A. U.

Experiment 1: This experiment lasted from December 5 to December 6. The record showed a fairly steady base line (with fluctuations not greater than ± 8 mv. during the day, and ± 4 mv. during the night). There were some slow undulations occurring at mealtimes which were more marked on the upper circuit. These never exceeded ± 5 mv. on the lower circuit.

Experiment 2: A second test was made on this subject (December 27 and 28). Here the record was a little more unsteady, showing slow changes in base line of ± 10 mv. during the day and ± 4 mv. during the night. Again, as in Experiment 1 on this subject, changes associated with periods of digestive activity were recorded on the upper circuit. This time these were as large as ± 20 or 30 mv.

CONTROL CASE 2.—Mr. D. G.

This experiment ran from December 28 (11 A.M.) to December 29 (5 A.M.). Throughout a period of eighteen hours the record was remarkably steady except for a short episode during which changes were made in the machine by the operator.

CONTROL CASE 3.—Dr. L. E.

This subject was tested from January 3 to January 4. For a period of ten hours the record was flat within ± 5 mv. Then during the next four hours there occurred a very slow rise of potential of about 30 mv. Following this gradual increase there was a decrease to the base line within the space of four hours. This change took place during sleep and was more marked on the lower circuit. The difference of potential between the two upper electrodes remained perfectly steady throughout the experiment.

B. Female Controls.—CONTROL CASE 4.—Mrs. J. S., aged 67 (29 years past the menopause). This patient was connected to the machine on the fourteenth day after a vaginal hysterectomy and perineorrhaphy. Throughout the period February 5 to 9 the record was fairly steady, showing long, slow changes not exceeding ± 10 mv.

CONTROL CASE 5.—Mrs. A. C., aged 47 years.

This patient was tested from April 5 to April 8 (on the sixth to the ninth day after a left trachelorrhaphy). She was connected to the recorder on the seventh day of her menstrual cycle and so was in the nonovulating phase. It may be noted that her endometrium on March 30 was of the late secretory type.

This record does not show any remarkable changes in potential, except for the fact that, whereas during the day the changes were of a magnitude of ± 10 mv., the curve shows a definite flattening at night with changes of less than ± 5 mv. There seemed to be some variation of potential (15 to 20 mv.), associated with mealtimes, appearing on the upper circuit. On two occasions sharp changes (10 to 15 mv.) occurred when the patient voided.

CONTROL CASE 6.—Mrs. M. B., aged 65 years. This patient had passed the menopause twenty years previously. She was tested for four days during recovery from a Fothergill plastic operation performed on April 9. The experiment was started on April 15 and ended on April 19.

For the first two days the record did not show anything remarkable. The remainder of the record had to be discarded because these particular electrodes, due perhaps to drying, offered too high a resistance for the recording device.

EXPERIMENTAL RESULTS

I. Electrical Changes.—When the potential differences between two points of the pelvic region, i.e., between the vagina and the abdomen, or between the right side and the left side of the abdomen, were plotted against time, curves of two markedly different shapes were obtained in experiments on nine normal women during their estimated ovulation time.

In four patients (Cases 1, 3, 4, and 8) there was an abrupt increase of the difference of potential from a fairly constant base line (Figs. 1 and 2). The descent from the peak of the curves was fairly prompt and direct; the curves thus resembled an inverted V, which was more or less open, and as a rule rather symmetrical.

In five other patients (Cases 2, 5, 6, 7, and 9) the curves, after a similar abrupt rise, showed a rather extended plateau, and the regression from the maximal difference of potential was less abrupt than was its establishment. Hence these curves more closely resembled an inverted U.

The potentials recorded in these two groups showed wide variations in magnitude, duration, and sign.

a. Magnitude: With the exception of one case (Case 1) in which there was some doubt as to the absolute degree of potential increase (page 736), the changes recorded varied from 24 to more than 80 mv.

Study of all the records seems to indicate that the internal circuit has different properties in the various cases, for one gets the impression that when a fairly steady base line is obtained the gross change is usually smaller than when there are large oscillations in the base line.

b. *Duration*: In the first group of four patients (peaked curve), the time required for the attainment of the maximal difference of potential varied from about thirty minutes to eight hours, and the regressions of these potentials showed equally wide ranges.

Within the second group (exemplified by the plateau or inverted U-type curve), the time required for the complete rise and fall of the potentials also varied considerably. The duration of the increase seemed fairly constant (one-half hour to

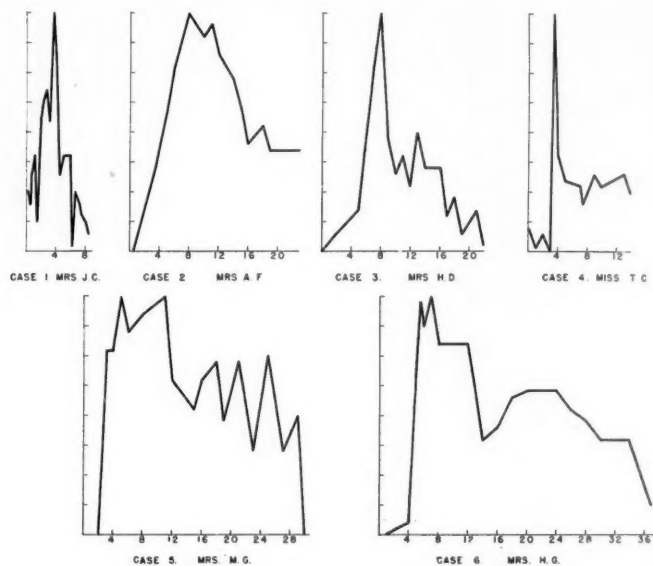


Fig. 1.*—Curves of ovulation potentials.

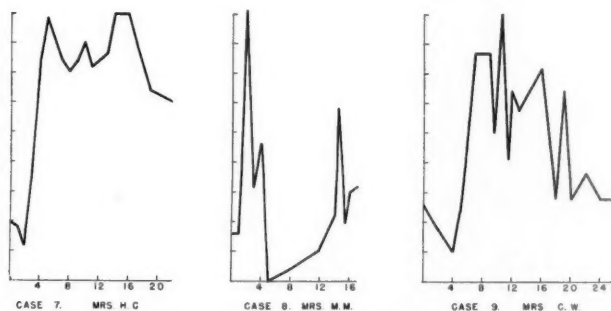


Fig. 2.—Potentials within estimated ovulation time. Mature follicles without rupture.

three hours). The duration of the plateau phase varied from five to twelve hours. The regressions of the potentials also showed wide ranges.

c. *Sign*: In 4 cases where a vaginal-abdominal circuit was employed, with the abdominal serving as reference electrode, the vagina became negative in 3 cases (Cases 5, 7, and 9), and positive in one case (Case 2).

*All curves are plotted as though changes were on the positive side of the reference axis. Figs. 1 and 2 show only the shape of the curve in each case. Each curve has been multiplied by a factor so that the maximum amplitudes are identical. This defines the curve characteristics more clearly. The time relation has been respected. The exact magnitude of potential change is given in the text. Abscissae in all cases are in hours.

If we assume that the active ovary was the one containing a ruptured follicle, or a mature follicle, we find, by using surface electrodes, that, out of 4 cases, the active ovary became negative in 2 cases (Cases 3 and 8), and positive in 2 cases (Cases 7 and 4). However in one of these we had evidence that both of the ovaries were fairly active (Case 4) (Table I).

TABLE I. POTENTIAL CHANGE AND FOLLICULAR ACTIVITY

CASE*	POSITION OF ELECTRODES	MAGNITUDE OF BASE LINE OSCILLATIONS MV.	POTENTIAL CHANGE ASSOCIATED WITH FOLLICULAR RUPTURE OR MATURATION MV.	OVARIAN FINDINGS	SIGN OF POTENTIAL CHANGE IN VAGINA OR OVER ACTIVE OVARY
2. Mrs. A. F.	Vaginal-abdominal	± 5	+30	Ruptured follicle in right ovary	Vagina positive
3. Mrs. H. D.	Surface†	± 5	+24	Old corpus luteum in left ovary	Left ovary negative
4. Miss T. C.	Surface	-10 to +16	+80	Young corpus luteum in right ovary, as well as one apparently mature ovum; left ovary contained two apparently mature ova	Right ovary positive
5. Mrs. M. G.	Vaginal-abdominal	± 5	-24	Ruptured follicle in right ovary	Vagina negative
7. Mrs. H. C.	Surface	± 4	-34	Mature unruptured follicle from left ovary. This contained an ovum which vigorously attracted spermatozoa in vitro	Left ovary positive
	Vaginal-abdominal	± 3	-10		Vagina negative
8. Mrs. M. M.	Surface	± 10	-60 -40	Largest follicle in right ovary	Right ovary negative
9. Mrs. C. W.	Vaginal-abdominal	± 5	-25	Large follicle resected from right ovary. This contained an ovum which had recently suffered atresia	Vagina negative

*The first case (Mrs. J. C.) was omitted here because polarity was unfortunately not determined.

†In all cases where surface electrodes were used the left electrode was the reference electrode, so that a change of +24 mv. means that the right electrode was 24 mv. positive to the left.

II. *Correlation of Ovulation with Electrical Changes.*—Of these 9 cases, 5 (Cases 1 to 5 inclusive) were discovered at laparotomy to have ovulated at about the time the potential difference increased. In Case 6 ovulation was placed near this time by the advent of catamenia on the 15th day following the rise in potential. Significantly in the other three women (Cases 7, 8, and 9) the typical potential change was observed, though subsequent laparotomy showed that ovulation, while apparently imminent, had not yet occurred. From one of these patients (Case 7) an ovum which was strongly attractive to spermatozoa was obtained by aspiration of the ripe follicle. Also in Case 9, by aspiration of a follicle which appeared mature on gross examination, an elliptical ovum was recovered. This, perhaps because of faulty in vitro technique, or because of endogenous degenerative changes, did not attract spermatozoa.

DISCUSSION AND CONCLUSIONS

Of prime practical importance are the following questions: What is the time relationship between this observed electrical sign and liberation of the ovum? Does the electrical effect precede rupture? Are the two events synchronous, and is the potential change perhaps caused by the rupture of the follicle? Or does the electrical sign follow rupture?

From our present studies we are led to believe that the electrical change which we have recorded does not follow rupture, nor is it necessarily coincident with it, which we first believed to be the case, and as is true of the change which has been observed in the rabbit. The increase in potential difference may, as in Cases 7, 8, and 9, precede ovulation, and perhaps it always does. That recently ruptured follicles were found in Cases 1, 2, and 4, within twelve hours, and, in Case 5, twenty-four hours after the swing was completed, indicates that if the change in potential precedes the event it does so by only a few hours. When we know more of the development of the corpus luteum, we may judge its age more accurately, and in this way be better able to place the time of ovulation. At the present time it is only possible to characterize this body as (1) *of recent inception*, when the stigma of rupture is still apparent; (2) as *young*, while the coagulum remains and the centripetal capillaries have not yet engrossed all free erythrocytes; and (3) as *mature*, when the luteinized folds appear as solid tissue masses bounded on the periphery by the theca externa, and centrally by a thin layer of modified cells of the theca interna.

Rogers⁹ has shown that in the rat somewhat similar electrical changes are synchronous with exit from estrus. Young and Blandau³ emphasize the fact that "in domestic animals as the horse, the cow, the ewe, the sow, and the guinea pig, in which ovulation is spontaneous, it has been found to occur late in the period of heat or *even shortly after its end*" (italics ours). Does this occur in human beings, too, and are these differences in potential caused not solely by the single event of follicle rupture, but rather by a more generalized phenomenon?

It is true that in some of these cases the exceedingly long duration of the process (more than twenty-four hours) seems to point toward a general modification which appears and disappears slowly. There

is, however, no doubt that a local process must occur which is associated with sharply localized potential changes, since we are able to record large differences of potential between 2 nearby points, *a* and *b*, which changes are not recorded between 2 other points, *c* and *d*, no further from the first 2 than are these from each other.

This deduction has been checked by experiments on animals which will be reported later. If a difference of potential is applied across two small silver-silver chloride plates placed anywhere in the peritoneal cavity, the potential changes are recorded with electrodes placed on the skin, and these changes show a strong maximum in the neighborhood of the plates. It seems therefore probable that if, in the experiments reported above, we are dealing with a more general phenomenon (estrus), we are recording its strongly localized (probably ovarian) manifestation. The differences in magnitude, or even in sign, of the potentials recorded would be easy to explain on this basis. On the other hand, the exact relationship between the actual rupture of the follicle and the recorded potential changes constitutes a question which we are at present not in a position to answer with certainty.

Limited as these experiments are in number and duration, they strongly indicate that associated with human ovulation there is a characteristic change in the electrical condition in the pelvis which has not been observed at other times in these cases, or at any time in subjects who have no ripe follicles. So far this change has been identified as an increase of the preceding and succeeding differences in potential between two pelvic electrodes.

It is interesting to observe that a curve suggesting ovulation occurred in all nine cases during the time expected on the basis of current theories of ovulation time.

We wish to acknowledge the valuable assistance rendered by Mr. L. Kingsland (S.B.) in the course of this investigation.

REFERENCES

- (1) Pincus, G.: *The Eggs of Mammals*. The Macmillan Company, 1936.
- (2) Allen, E., Pratt, J. P., Newell, Q. U., and Bland, L. J.: *Contrib. Embryol. (Carn. Inst. Wash.)*. 22: (127): 45, 1930.
- (3) Young, W. C., and Blandau, R. J.: *Science* 84: 270, 1936.
- (4) Hartman, C. G.: *AM. J. OBST. & GYNEC.* 7: 40, 1924.
- (5) Burr, H. S., Hill, R. T., and Allen, E.: *Proc. Soc. Exper. Biol. & Med.* 33: 109, 1935.
- (6) Reboul, J., Friedgood, H. B., and Davis, H.: *Am. J. Physiol.* 119: 387, 1937.
- (7) Burr, H. S., Musselman, L. K., Barton, D. S., and Kelly, N. B.: *Science* 86: 312, 1937.
- (8) Rock, J., Reboul, J., and Wiggers, H. C.: *New Eng. J. Med.* 217: 654, 1937.
- (9) Rogers, P. V.: *Am. J. Physiol.* 121: 565, 1938; *Endocrinology* 22: 35, 1938.
- (10) Rubenstein, B. B.: *Endocrinology* 22: 41, 1938.
- (11) Burr, H. S., Lane, C. T., and Nims, L. F.: *Yale J. Biol. & Med.* 9: 65, 1936.
- (12) Rock, J., and Bartlett, M. K.: *J. A. M. A.* 108: 2022, 1937.

DISCUSSION

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—The determination of electrical characteristics of the living system has been speeded up by the development of a vacuum potentiometer to measure minute voltage changes in living systems. Through the use of this mechanism it is now possible to determine in experimental

animals and human beings the external signs of ovulation. The work of Burr, Hill, and Allen on the rabbit has been confirmed and extended to human beings to the extent that the time of rupture of the Graafian follicle may be very closely determined.

Of academic interest in connection with this discovery will be the correlation of the state of the endometrium and the characteristics of the vaginal smears at the time ovulation occurs, and the findings as to the hormone content of the blood and urine in relation to this definite expression of ovarian function. Other metabolic phenomena, such as the temperature and basal metabolism, shown by Rubenstein to reach a low midcycle point may be restudied in connection with this new method. Of scientific interest also will be the assembling of a definite histologic picture of the progressive changes in the ovary in conjunction with the formation of the corpus luteum. From such studies based on the exact time of ovulation may be settled finally the theory of luteinization and the origin of the lutein cells. From Dr. Rock's present finding, I take it, he ascribes the lutein cells to the theca interna. Similar studies to those of Rogers in the rat may determine the effects upon maturation of the follicle, injections of hormones or other stimulating agents.

In relation to sterility the determination of the exact time of ovulation is important, in that it will afford an opportunity to determine the optimum time for coitus or artificial insemination or to determine the biological attractiveness of an ovum to the semen of a mate. As far as contraception is concerned, the exact time of ovulation may lead to further advances of our knowledge of the fertile period. Probably further developments and continuance of this mode of investigation will lead to the discovery of other changes of the electrical potentials of the pelvic organs during menstruation or at the onset of labor, or may determine for us the recurrence of ovulation during lactation, and the character of ovulation following hysterectomy. Whether the reaction as expressed by a broad curve is a result of estrus, a general phenomenon, or whether the reaction expressed by a sharp peak is due to ovulation itself alone as a local change seems as yet undetermined.

DR. R. A. ROSS, DURHAM, N. C.—Dr. Rock has mentioned the type of endometrium of one patient, and I would be interested to know whether endometrium was studied routinely and by what procedure? I am also anxious to know if he was able to obtain the ova in each instance. We have employed the technique as described by Newell, Pratt, and Bland with discouraging results.

The description of a corpus luteum given by Dr. Rock is pertinent. Yet we must remember at all times the warning of Hartman as to the unreliability of the appearance of the corpus luteum as an index of its age.

DR. ROCK (closing).—The endometrium was obtained in most of the cases, and in one of them, as I said, it showed the effect of a long progestin influence. The cases in which freshly ruptured follicles were found usually showed the endometrium characteristic of the late proliferative phase. There were no cytologic changes which we could attribute to early progestin influence.

The difficulty of dating the corpus luteum derives from the fact that the luteinization is apparently a progressive process which starts before rupture. At least changes resembling those of luteinization occur in the theca and progress to true luteinization. We have to date our corpus luteum from these changes; i.e., from the thickness of the cell layer, and especially the degree of vascularization. At first there are many open spaces filled with extravasated blood cells which later become lined with endothelium.

We, too, have attempted to recover ova from the tubes but have not been very successful. Once we recovered something which looked like an ovum. I think the difficulty is merely a matter of technique.

I would like to add that we had some controls of these cases. We tested two women who were past the menopause, and another woman during the first week of her cycle, and failed to obtain any curves resembling those which I have shown. Three healthy young males also showed no signs of ovulation.

ADVANCES IN OUR KNOWLEDGE OF THE EARLY PRIMATE EMBRYO*

GEORGE L. STREETER, M.D., BALTIMORE, MD.

SUMMARY†

WHEN the three germ-layer theory was perfected by von Baer, it was thought that the fundamental parts concerned in the organization of our body tissues had been found and the ectoderm, mesoderm, and endoderm shown in his beautiful drawings were the three ultimate materials from which our various organs are derived, the three layers being regarded as homogenous in themselves and homologous in all animal forms. This concept seemed to simplify the teaching of embryology and during the subsequent hundred years embryologic and anatomic thought has been dominated by this three-layered topographic analysis, and with a certainty like that formerly prevailing among physicists and chemists regarding the indivisibility of the atom.

As happened with the atom, it is now becoming apparent that the three germ-layer theory in its original diagrammatic form cannot be harmonized with various embryologic observations which have recently been coming from different sources. Improved technique and greater expertness in handling the material have provided us with earlier embryonic stages of the higher mammals including man and monkey, and we can now study under our microscopes beautifully prepared material of a period of development heretofore almost wholly unknown.

We are finding that prior to the laying down of the so-called three germ-layers a more fundamental thing has already taken place, namely, the materials that are to form the envelopes and mechanisms for the attachment and nourishment of the embryo have been separated from the materials that are to form the embryo itself. That is, the developing ovum is composed, on the one hand of "formative substances," to use Hubrecht's term, and on the other hand of "auxiliary substances" which play but a temporary role and are discarded at birth. The segregation of these latter "auxiliary substances" and their precocious differentiation in the form of a trophoblastic shell appear to be the principal results accomplished by the subdivision of the original one-celled egg into a structure consisting of many small cells. This phenomenon of cell-cleavage and the setting apart and precocious differentiation of the auxiliary substances constitutes a fundamental and initial chapter in the development of the embryo.

*Read, by invitation, at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

†NOTE: This is a brief summary of a more extended paper by the author in a future issue of *Contributions to Embryology*, published by the Carnegie Institute of Washington.

On the eighth day while the ovum is still a free blastocyst the auxiliary cells are already distinctly set apart from the small group of true embryo cells which, having divided but a few times, are still large and retain their primitive unorganized blastomere character. This eighth day marks the completion of what may be regarded as the first and thus the most fundamental stage in the development of the ovum.

There then follows the awakening of the embryo-forming cells which is expressed by proliferation and arrangement of its cells into an ectodermal disc. In the orientation and organization of this embryo or germ-disc it becomes set-off, both dorsally and ventrally by fluid-containing clefts from the abutting auxiliary tissues. The dorsal cleft is first to appear and as it enlarges with the increase of its fluid

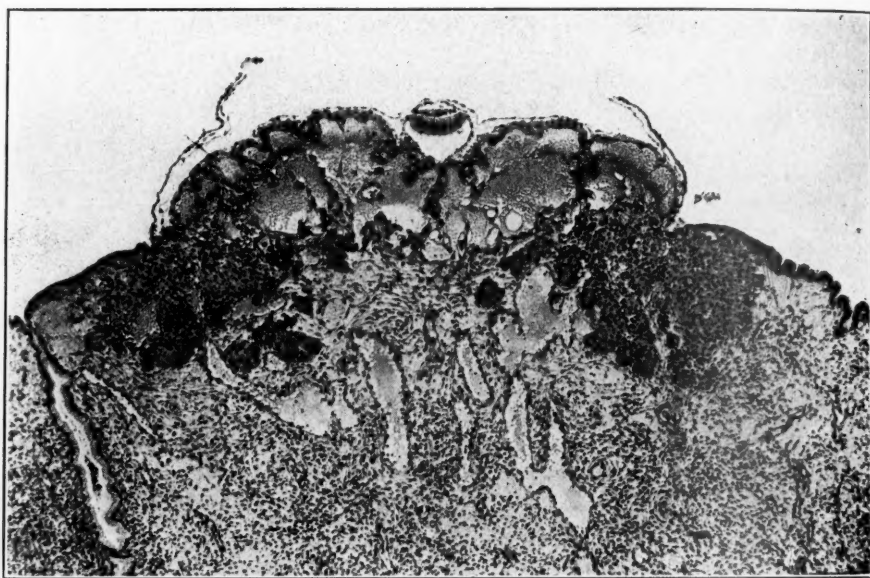


Fig. 1.—Implantation of the rhesus embryo as it appears on the thirteenth day. The trophoblastic lacunae are filled with maternal blood and in the immediate neighborhood there is a marked proliferation of the maternal epithelium upon which the trophoblast feeds. Note distention of capillaries. Enlargement 50 diameters. Embryo No. 562.

we recognize it as the amniotic cavity, and its boundary cells are soon fashioned into an amniotic membrane. Similarly, the ventral cleft enlarges to become the combined gut and yolk-sac cavity.

As for the yolk-sac we have seen that it is something more than an embryonic vestige. Furthermore, the yolk-sac does not bud off from the inner cell mass in the form of a solid clump of cells, thereafter acquiring a central cavity, as had been supposed. Nor is it at any time an intrinsic part of, or homogenous with, the gut tract. Instead, the earliest cells of the yolk-sac are differentiated as a thin membrane between which and the gut endoderm there arises the conjoint yolk-sac cavity and gut cavity. This cavity is therefore dual in origin. It

is bordered on its dorsal part by cells that are to form the gut endoderm, an induced product or migratory element from the embryonic ectoderm. Whereas, on its ventral part, it is bordered by the yolk-sac endoderm, which is not an embryonic disk derivative but belongs to the group of auxiliary tissues. The gut and yolk-sac are thus different in origin and are always abruptly demarcated from each other. The one becomes a definite part of the embryo and the other is an auxiliary organ which in primates plays a temporary but probably an essential role in the metabolism of the embryo until the time when its functions are taken over by the placenta, a much more elaborate and efficient organ. Its growth is then arrested, but we can still find its degenerate remnants in the fetal membranes at birth.

Without resort to hypothetical stages or diagrams we have traced the formation of the trophoblastic shell and its implantation. We have seen the setting apart of the amnion and yolk-sac. There remains only the further development of the embryo proper and the formation of its intrinsic organs. It is at this point if you so choose, that the ancient and honorable three germ-layers can be dragged in. But even so I must warn you that they had better be confined to the embryo itself. For any such mechanical analysis is of no help whatever in the understanding of these auxiliary elements of the ovum whose interesting history we have been reviewing.

THE INFLUENCE OF LONG-CONTINUED INJECTIONS OF ESTROGEN ON MAMMARY TISSUE*

LUDWIG A. EMGE, M.D., AND K. M. MURPHY, M.D., SAN FRANCISCO,
CALIF.

(From the Department of Obstetrics and Gynecology, Stanford University School of
Medicine)

A NUMBER of recent experimental studies leave no doubt that *under certain conditions, yet undefined*, sex hormones can awaken a latent impulse capable of inducing malignant changes in a substratum hereditarily susceptible to cancer. The far-reaching importance of such a possibility has led to the issuance of warnings against the empirical use of female sex hormones. While such warnings are timely and well meant, they are prone to create the impression that what strictly applies to animal experimentation applies also to man. However, laboratory findings, until proved applicable, should not be interpreted clinically, but should be viewed strictly in the light of species and strain susceptibilities of the particular animals and tumors studied. In order to clarify the situation, the carcinogenic specificity of sex hormones must be determined and many types of benign and malignant tumors must be studied. This is a difficult task, complicated by a multiplicity of factors. It has been somewhat simplified by the isolation and chemical determination of sex hormones, but there still remains a formidable array of obstacles to be surmounted before the hormone-cancer relationship is better understood.

While a knowledge of the chemistry of the sex hormones is indispensable for an understanding of our problem, we cannot at this time go into a detailed account of their relation to carcinogenic agents.[†] Suffice it to say that the sex hormones belong to the widely distributed group of hydrocarbons of which there are many, ranging from simple anthracene to complicated forms including vitamins, bile acids, sterols, heart poisons, saponins, the morphine group, and the carcinogenic hydrocarbons. It is the relation to this last group that assigns to them a sinister rôle. It is important to know that carcinogenic agents of the hydrocarbon group possess estrogenic properties, just as certain estrogenic substances possess carcinotropic properties. It is of interest that estrogen is chemically related to the sterols, and that the latter may be changed into carcinogenic agents by a process of degradation. The significance of this is evident, since both female and male sex hormones

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

Supported in part by a grant from the Committee on Scientific Research of the American Medical Association.

†For a detailed account, see L. F. Fieser's *The Chemistry of Natural Products Related to Phenanthrene*, published by Reinhold Publishing Company, New York.

may be obtained from cholesterol. However, only certain chemical components belonging to the estrogenic group so far have shown carcinogenic potentialities and that, only in cancer-susceptible, small laboratory animals (mainly mice). Male sex hormones possess either none or very little of this characteristic, but since they also can be broken down into estrogen by a process of degradation and since sex hormones in general are structurally related to cholesterol, which in turn is related to the most powerful carcinogenic hydrocarbon—methyl-cholanthrene—estrogen as a carcinogenic factor deserves careful consideration.

Until certain endocrine problems were clarified, the study of the hormone-cancer relation was greatly handicapped and consequently slow in developing. In theory, it antedates modern endocrinology by many years, since it really received its inception in 1889 when Schinzinger suggested that mammary cancer might be retarded by the ablation of the ovaries. However, fundamental research of this problem began only in 1907, when Loeb reported that in certain strains of mice practically all males were free from breast cancer, while the incidence was very high in the females. Nine years later, Lathrop and Loeb made an observation which, in the light of Schinzinger's suggestion, is very interesting. They reported that the tumor incidence in mice subject to mammary cancer could be decreased in direct proportion to the time of castration, and this has been confirmed by Murphy and Sturm, and Cori. Lathrop and Loeb found that *early* castration would markedly reduce the cancer incidence in the females, and in fact would almost nullify it. These experiments emphasized the importance of the age factor, for if castration were postponed until the eighth or tenth month of life malignant growth could be retarded but slightly. An attempt to offset the influence of castration by the grafting of ovaries from related animals failed (Loeb, Cori). However, Murray demonstrated in 1928 that this could be achieved by using ovaries from sisters. He blamed previous failures to strain differences not sufficiently eliminated by inbreeding. In his experiments, cancer-resistant males were implanted after castration with sister ovaries, resulting in 7.1 per cent of cancer in these otherwise cancer-immune males. Murray also demonstrated that in the strain of mice used by him *virginity* markedly decreased the tumor incidence. His castration experiments verified the conclusions of Loeb and Cori.

In our experience with more than 5,000 transplantable mammary tumors of the white rat we have observed a variety of responses to castration. For instance, certain fibromas and adenofibromas would not grow before sex maturity unless the animals had been castrated or continuously injected with estrogen. While this conforms with the results of others, the character of the tumor must be taken into consideration. We found that certain mammary sarcomas were not influenced by the age of the host, since they could be transplanted into young or old rats with equal ease regardless of castration. Recently Sauerbruch and Knake also reported an increase in cancer susceptibility in rats after castration. It must be considered, however, that spontaneous

and transplanted tumors may respond differently to the same biologic condition, although both types furnish equally valuable information in controlled experimentation.

In 1929, when both Doisy and his co-workers and Butenandt isolated estrus-producing hormones in a pure form, they opened up a new field, not only for endocrinology but for cancer research. Lacassagne, applying this new knowledge, reported in 1932 that male mice ordinarily immune to breast cancer would develop this disease following the prolonged administration of estrogen, although not to the same extent as the females, a very high percentage of which produced mammary cancer under ordinary conditions. Lacassagne, therefore, is the first to link a particular sex hormone with a certain cancer in mice, demonstrating the correctness of the deductions of earlier investigators. His work, since confirmed by others (Burrows, Bonser, Gardner and others, Cramer and Horning, Loeb and others), has stimulated a very active search for further information on the relationship of endocrines to tumors. Lacassagne, among numerous other observations, has since reported that not all estrogenic substances have the same carcinogenic potentialities for cancer-susceptible mice. For instance, *estrone* possesses more of this quality than *equiline*, and *equiline* more than *equilenine*. He also reported that a combination of *estrone* and hypophyseal extracts would occasionally produce a malignant tumor in mice otherwise refractory to cancer. Lacassagne's conclusions suggest that the carcinogenic potentiality of *estrone* might be part of a biologic mechanism involving the hypophysis. The relation of the hypophysis to tumor growth has been studied by various investigators, and has been discussed by us previously (Emge and Murphy).

Experimental investigations so far cited demonstrate beyond doubt that the female sex gland bears some relation to tumor genesis in a strictly limited field. However, there is as yet no proof that estrogenic substances are carcinogenic agents in an unqualified and general sense. We point this out in order to emphasize that whatever carcinogenic attribute is contained in estrogen must be of a highly specialized nature, capable of acting as a carcinogenic or carcinotropic agent only under certain genetic conditions and, as far as is known, only in tissues directly dependent upon this hormone for functional activities. This is particularly true of breast tissue, which requires estrogen besides other hormones for proper function. Various attempts have been made to determine just how much estrogen is necessary for normal function of the breasts but nothing definite has been learned, although it was observed that the amount of estrogen necessary to stimulate hyperplasia of the breast is generally limited and cannot be pushed beyond a given point (Taylor). This has been confirmed by Howard, who studied proliferative activities of the mammary gland of rats under the influence of acid extracts of pregnancy blood in our laboratory.

The normal estrogen level in living tissues and body fluids apparently is a very variable quantity subject to great fluctuations. Since there is no criterion to serve as a guide, it is not clear to us what is meant by an *excessive* amount of *estrogen* in the blood or tissues. This applies to the statements of Laqueur and others, P. Engel, Dingemanse and others, and Loewe and others, who reported an *excess of estrogen* in the blood of cancer patients and tumor-bearing animals. The same applies to the significance of estrogen levels in tissues. Lewis and Geschickter,

and Heiman and Krehbiel reported the presence of excessive amounts of estrogen in pathologic breast tissue of women and tumor-bearing rats, but neither Frank and his co-workers nor Mohs could confirm this. Frank, Goldberger, Salmon, and Friedman found that normal muscle tissue could store estrogen without showing unusual growth activity, and Mohs reported that the estrogen content of mammary adenofibromas of the rat was very low and could not be increased by the continued injection of estrogen. He expressed doubt that the growth ability of the mammary adenofibroma used by him was dependent upon a concentration of estrogen in the tumor tissue, and Frank and his co-workers warned against making general conclusions on the sole basis of finding estrogenic substances in abnormal tissue because this may be only a normal occurrence similar to that of glycogen storage in muscle, which is increased or decreased as conditions demand.

A number of attempts have been made to extend the principle of Lacassagne's experiments to other tissues and animals. McEuen showed that estrogen, like other carcinogenic agents, could produce endometrial hyperplasia, but not malignancy, in rats. Overholser and Allen, and Hisaw and Lendrum observed, after prolonged estrogen administration, the formation of lesions on the monkey's cervix which resembled very early malignancy, but since these lesions disappeared after estrogen was discontinued, or was neutralized by corporin (corp. lut.), it is safe to assume that cancer was not actually produced.

Several investigators have attempted to create a favorable state for hyperplasia to be acted upon by estrogen by resorting to mechanical or biochemical traumatization. Overholser and Allen did so with the monkey's cervix, with the result reported. Burrows combined tarring and estrogen administration and reported that the resulting tissue proliferation and metaplasia *rarely* reached a cancerous state if the animals were refractory to tarring. Perry and Gintzon applied a combination of 1:2:5:6 dibenzanthracene and estrogen to the skin of mice, which was followed by the appearance of numerous benign and some malignant tumors. These are interesting experiments but the introduction of several factors unfortunately beclouds the issue and therefore sheds no light on the specificity of estrogen as a carcinogenic agent.

In 1934 Engle and Smith, and more recently Suntzeff, Burns, Moskop, and Loeb, reported that prolonged administration of estrogen to susceptible mice leads to proliferative changes in the cervix and vagina which are not unlike carcinomatous degeneration. These very extensive and thorough studies led the authors to conclude that the changes observed are not compatible with the view that somatic mutations in the stimulated tissues are the immediate cause of their cancerous transformation. In confirmation Gardner, Allen, Smith, and Strong described the appearance of tumors in or near the cervix of cancer-susceptible mice after prolonged administration of large doses of estradiol benzoate. Since one of these tumors proved to be a transplantable carcinoma, the significance of this finding is evident. MacDonald, as well as Howard, attempted to produce unusual cell proliferation in the breasts of rats and rabbits by prolonged administration of estrogen, progesterin, pituitary extracts, and pregnancy blood, but reported that no malignant changes resulted. Bischoff and Maxwell failed to influence the behavior of transplantable mouse sarcoma and mammary carcinoma by similar methods. That deciduomas can be pro-

duced by prolonged injection of corpus luteum extracts (Nelson and Pfiffner) is to be expected, and adds nothing to the knowledge of the relation of tumor production to sex hormones. Witherspoon's deduction that uterine fibroids are due to hyperestrinism resulting from cystic ovaries is also interesting, but cystic ovaries do not necessarily accompany fibroids. His report that endometrial hyperplasia was the precursor of fibroid tumors in 44 patients observed for a number of years is of more importance. It is generally assumed that endometrial hyperplasia is related to hyperestrinism, and since fibroids ordinarily shrink after the menopause, it is logical to link these tumors with some form of estrogenic imbalance. The mechanism probably is not as simple as that, because if fibroids and mammary cancer result from prolonged hypersecretion of estrogenic substances, why does not breast cancer occur oftener in women growing fibroid tumors of the uterus?

As far as the carcinogenic factor in estrogen is concerned, no more can be said at present than that estrogen increases the incidence of mammary cancer in certain strains of susceptible mice and occasionally in rats (Gardner and others, Burrows, Bonser, Cramer and others, Suntzeff and others), and that in these animals it can incite cancerlike tissue proliferation of the cervix and vagina (Engle and Smith, Suntzeff and others) but only occasionally produces a true cancer (Gardner and others). None of these observations prove that estrogen is the sole factor involved, and as far as small animals are concerned, one may even go so far as to state that it is possible that estrogen becomes a carcinogenic factor only when a hereditarily prepared substratum for cancer exists. Nothing is known of the effects of prolonged administration of estrogenic hormones in human beings. Mazer and Israel recently reported a fairly large series, and there is nothing in their report to indicate that tumor growth was stimulated. However, since Loeb pointed out that the effect of hormones on tumor production in experimental animals may be delayed, it is very worth while keeping an eye open for untoward effects in clinical medicine, particularly in relation to breast reactions. So far, we have never seen an aggravation of cystic disturbances of the breast during treatment with estrogenic or chorionic hormones. In fact, these hormones commonly relieve the discomfort of the patient and cysts frequently diminish in size. However, the effect of any female sex or chorionic hormone on cystic breasts is variable and nonpredictable. Some breasts will not respond to one but to another, or vice versa, and therefore we doubt that the action of either is specific and direct.

Apparently the endocrine control of the mammary gland is equally as complicated as that of other secretory organs depending upon cyclic hormonal impulses. It is certain that the growth of this gland is dependent upon the ovary and probably responds to its stimulation in a direct ratio to the normal estrogen-progestin interchange. If estrus is prolonged, ducts may proliferate, as observed in the rabbit by Ancel and Bouin. However, in animals with short estrual phases such as occur in the rat, the cyclic response in breast tissue may be negligible. If the luteal phase is prolonged, as happens with sterile copulation, the mammary gland may show proliferative activities similar to those observed in the first half of pregnancy. Evans and Simpson noticed that after

injecting anterior pituitary extracts containing a luteinizing factor, rats' breasts would show a thickening of gland and lactating phenomena corresponding to changes seen in the latter half of pregnancy.

It is of further interest that the mammary gland of the male rat is usually limited to the development of ducts. We have found that implanting mammary adenomas from females into males leads to a disappearance of alveoli in many instances. Male rats show an insignificant estrogen level, although Turner demonstrated readily detectable amounts in the feces of certain males. Since the male has a paucity of estrogen and presumably a mammary gland free from cyclic changes, it occurred to us that the implantation into these animals of adenofibromas capable of certain mutations offered an excellent opportunity to study the effect of prolonged administration of estrogen* upon both the tumor and the host. We fully realize that the injection of hormonal substances may set up a trend of events quite different from normal occurrences, but since neoplastic tissue changes are not normal, this form of experimentation is at least not illogical. We are aware that chemically prepared endocrine substances may differ, and we are investigating this factor at present.

We have been studying the growth behavior of transplantable mammary tumors of the rat since 1929. As previously reported (Emge), our tumors have shown a remarkable ability to undergo mutations ranging from various types of adenofibromas to those of fibromas and fibrosarcomas. The mechanism underlying the changes occurring in the course of transplantation has puzzled us greatly, and in an attempt to unravel the complicated process, we have at various times resorted to experimentation along the lines of a hormone-tumor relationship. Our attention was first called to this when we surveyed the transplantability of certain of these tumors in 400 male and female white rats of the Wistar strain, and we found that successful transplantation was in direct proportion to age. Rats under sixty days of age, regardless of sex, rarely grew tumors. From the age of sex maturity (about 90 days) to 250 days, the percentage of successful "takes" reached its maximum, and decreased when the animal passed into the third trimester of its natural life. Old animals, also, were difficult to implant, but on further investigation we found this to be true only of benign tumors. Sarcomas derived from the latter were no respecters of age and could be grown at any age. Following this survey, we undertook a short study (1932), not published, in the hope of obtaining further information on the age factor in relation to the transplantation of benign mammary tumors. We implanted 45 animals 40 and 90 days old, some of which were castrated, with the same mammary tumor. After implantation, 50 units of theelin were injected daily under the skin of a certain number of castrates for 210 days. Control rats 40 days old failed to grow tumors, but those 90 days old did so in every instance.

*All experiments reported here were done with *aqueous* theelin (Ketohydroxyestrin), generously donated by Parke, Davis and Company through the courtesy of Dr. E. A. Sharp.

The results recorded in Table I suggest that estrogen bears a relation to implantability and growth of tumor implants. However, growth variations in the estrogen groups are too wide and the series too small to permit final conclusions.

TABLE I. PERIOD OF TREATMENT: 210 DAYS

	NORMAL CONTROL MALE AND FEMALE	CASTRATES MALES	THEELIN TREATED MALES	CASTRATE FEMALES	THEELIN TREATED FEMALES
Age: 40 days					
22 animals	5	6	3	5	3
Per cent takes	0	83	100	20	66
Daily tumor gain	0	+0.19	+0.03	+0.36	+0.21
Daily body weight change	+0.47	+0.45	+0.44	+0.44	+0.47
Int. units theelin			10,500		10,500

	CON- TROL MALES	CASTRATE MALES	THEELIN TREATED MALES	CONTROL FEMALES	CASTRATE FEMALES	THEELIN TREATED FEMALES
Age: 90 days						
23 animals	3	6	3	2	6	3
Per cent takes	100	50	33	100	83	100
Daily tumor gain	+0.44	+0.09	+0.02	+0.76	+0.10	+0.05
Daily body weight change	+0.12	+0.44	+0.31	+0.03	+0.37	+0.26
Int. units theelin			10,500			10,500
Daily injections: 50 I.U.						

Being occupied with other investigations related to the growth problems of these tumors, we did not undertake further estrogen studies until 1936, when we studied the relation of varying amounts of theelin given over long periods of time to animals implanted with a mammary adenofibroma of great growth potentialities (Emge, Murphy, and Schilling). This tumor has been transplanted by us for eight years and has maintained its adaptability to hormonal stimulation. As is readily seen from Figs. 1 and 2, it responds vigorously to the stimulation of pregnancy. However, when it is implanted into males, it tends to lose its alveoli, forms ducts, or transforms itself into a connective tissue tumor. By continuing transplantation it can ultimately change into a vicious sarcoma. We therefore wondered if hormones had any part in this process. We were particularly interested in finding whether an estrogenic hormone could arrest the change from adenofibroma to fibroma, and since none of our adenofibromas has ever produced a carcinoma in the ordinary course of transplantation we were interested also in learning whether estrogen could induce such a malignant change.

As previously reported (Emge and Murphy), we learned that rapidly repeated pregnancies create a marked hyperplasia in these tumors. We used this method in the hope of producing uncontrolled hyperplasia but came to the conclusion that neither the massive hormonal stimulation of pregnancy nor the long-continued storage of secretion would create an unusual hyperplasia, and that pregnancy was not a factor in producing or hastening the development of sarcomas. We found that the

massive hyperplasia, which subsided during puerperal involution, was entirely dependent upon the maintenance of the pregnant state (Figs. 3 and 4).

We next undertook a study of the estrogen content of various adenofibromas and their derivatives and found exactly as Mohs reported that neither adenofibromas nor sarcomas possessed an unusual estrogen con-

Fig. 1.

Fig. 2.

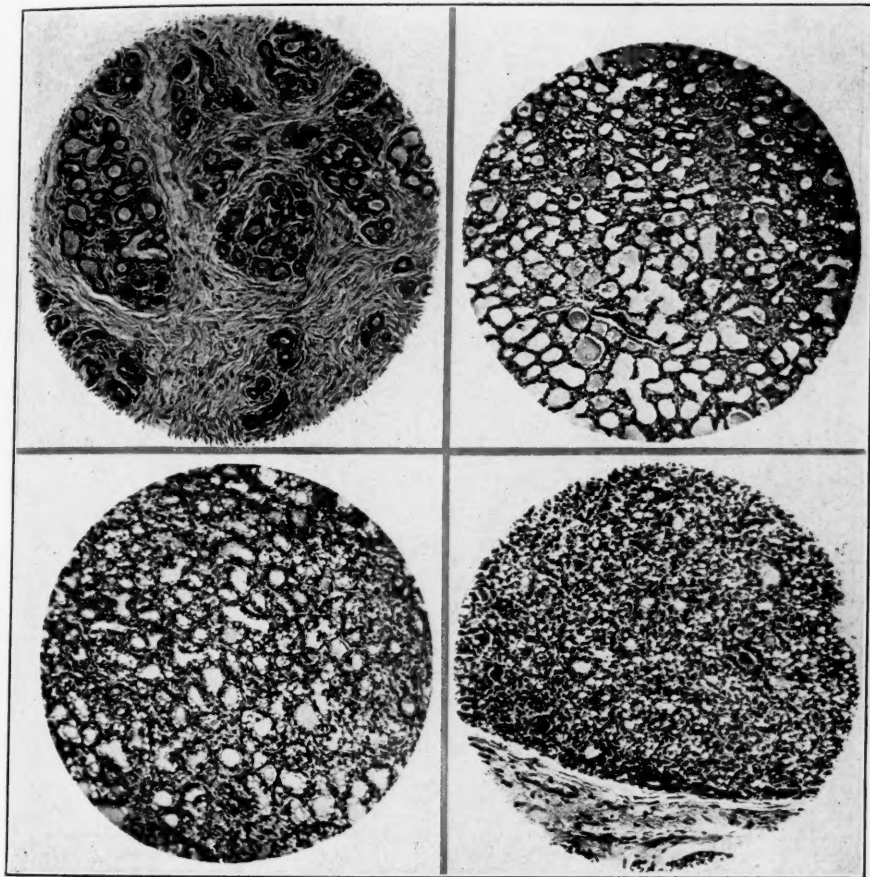


Fig. 3.

Fig. 4.

Fig. 1.—Control. Adenofibroma showing usual whorl type with a compact stroma.

Fig. 2.—Female seven days postpartum. Adenofibroma demonstrating lactation reaction of pregnancy.

Fig. 3.—Two pregnancies. Tumor removed at term. Adenofibroma showing massive hyperplasia of gland tissue and abundance of secretion.

Fig. 4.—Three pregnancies during tumor growth period. Tumor removed sixteen days postpartum. Adenofibroma with hyperplastic glandular epithelium. Basement membrane broken in some areas. Secretion and mast cells present.

tent. Dr. C. F. Fluhmann, who investigated the estrogen levels of these tumors for us, reported that prolonged administration of this hormone did not raise the estrogen level beyond that expected. We therefore

have here a mammary adenofibroma incapable of abnormal estrogen storage, possessing sarcomatous tendencies, but lacking the ability to produce carcinoma. We were then interested in determining what effect various dosages of estrogen administered over varying periods of time would have on this tumor when grown in males and females of

Fig. 5.

Fig. 6.

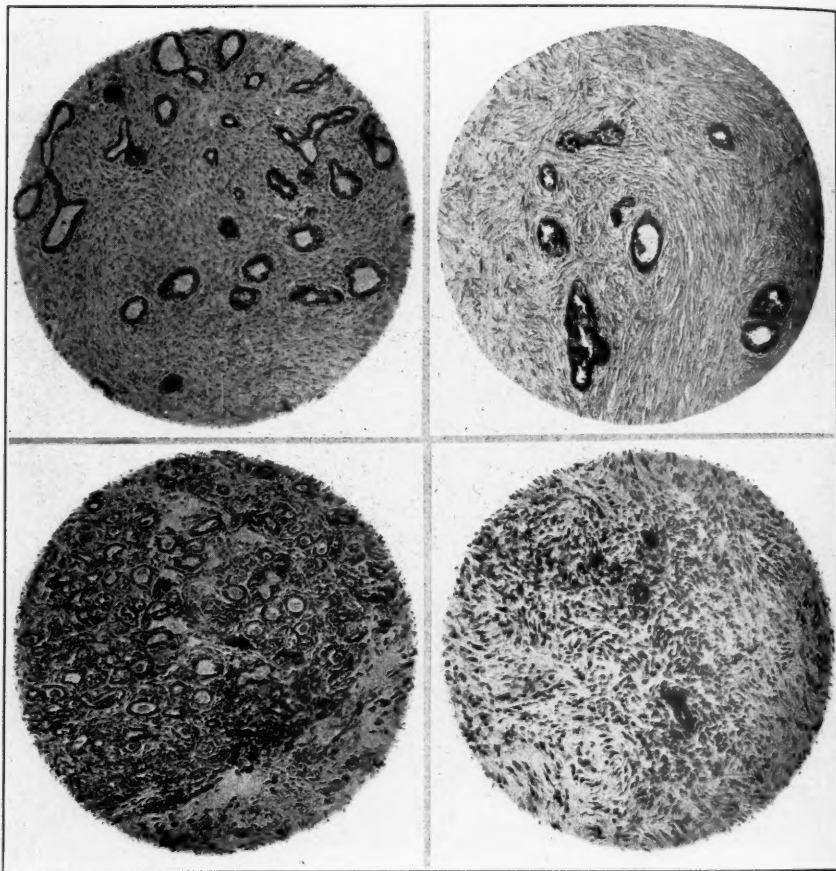


Fig. 7.

Fig. 8.

Fig. 5.—Female donor to Experiment 2. Diffuse adenofibroma.

Fig. 6.—100 I. U. theelin treated male of Experiment 2. Fibroadenoma showing reduction of glandular material. Demonstration of slight ductile proliferation. Stroma fibromatous, without unusual activity.

Fig. 7.—Female donor to Experiment 3. Adenofibroma with abundant glandular material. Secretion present. Five pregnancies during tumor growth span. Tumor removed five days postpartum.

Fig. 8.—Male control of third experiment. Adenofibroma showing a loss of glandular elements upon transplantation into males. Predominantly a pure fibroma with occasional small gland.

different ages. The particular rats used in this study are derivatives of the Wistar strain, in our possession since 1903, heavily inbred, and as far as we know, entirely free from spontaneous malignancies.

In designing our experiments we took into consideration the fact that a transplantable tumor may act differently from tissue growing in situ. In order to obtain information about such differences we not only studied the behavior of the transplanted mammary tumor but that of the normal mammary breast tissue as well. In the second experiment, 32 animals implanted with a diffuse adenofibroma* (Fig. 5) were divided into three groups, the first serving as controls, the second receiving 100 I.U., and the third 200 I.U. of theelin daily for 77 days. The tumors grew as indicated in Table II, with the usual variations in size, but no unusual growth behavior attributable to the injection of the estrogenic hormone could be demonstrated grossly. The animals receiving theelin showed a slight, but definite, loss in body weight (Emge, Murphy, and Schilling). In spite of the long-continued injections of estrogen, the tumors tended toward fibromas with a definite reduction of adenomatous material. Ducts showed a slight but unusual tendency to proliferate, and connective tissue elements showed no greater cellular activity than in routine transplantation (Fig. 6). In other words, the estrogenic

TABLE II. PERIOD OF TREATMENT: 77 DAYS

	CONTROL MALES	THEELIN TREATED MALES (100 I.U.)	THEELIN TREATED MALES (200 I.U.)	CONTROL FEMALES	THEELIN TREATED FEMALES (100 I.U.)	THEELIN TREATED FEMALES (200 I.U.)
Age: 140 days						
32 animals	5	6	6	5	5	5
Per cent takes	60	60	83	60	50	60
Daily tumor gain	+0.04	+0.05	+0.02	+0.46	+0.06	+0.11
Daily body weight change	+0.32	+0.13	-0.05	+0.25	+0.18	+0.17
Total Int. units theelin		8,000	16,000		8,000	16,000
Autopsy weights of:						
Testes	2.57	2.54	2.64			
Ovaries				0.076	0.086	0.084
Pituitary	0.012	0.010	0.010	0.010	0.011	0.012
Adrenals	0.048	0.031	0.025	0.066	0.042	0.050
Thyroid	0.055	0.052	0.048	0.040	0.037	0.040
Spleen	1.23	1.22	1.63	1.59	1.36	1.26
Liver	10.68	12.45	10.55	10.44	10.25	9.29
Kidneys	1.81	1.83	1.82	1.58	1.45	1.42
Daily injections: 100 or 200 I.U.						

hormone did not arrest the reduction of glandular tissue nor produce unusual hyperplasia, nor did it stimulate connective tissue to unusual activity.

Acting on Loeb's suggestion that the prolonged use of estrogen might prove more important than the dosage, a further experiment was done, in which 39 animals 160 and 300 days old were given 50 I.U. of theelin bi-weekly over a period of 163 to 368 days (see Table III). The tumor used for implantation showed abundant glandular material (Fig. 7). Neither age group showed any significant differences in the number of "takes," tumor growth rate, or daily tumor gain. The testes of the older animals weighed less and the adrenals more than the controls.

This was not so of the younger group, and the significance of this is not clear to us. In all of the injected animals, there occurred a marked decrease in the weight of the liver and a reduction in body weight, quite similar to that of the previous experiments. The tendency of the tumor to develop into a cellular fibroma and the general behavior of the glandular tissue toward duct formation at the expense of the alveoli were also observed in this series (Figs. 8 and 9). However, there was one 160-day-old injected male which developed a tumor of unusual hyperplastic tendencies. Essentially this affected the ducts but, as can be seen in Figs. 10 and 11, alveoli were also involved. There was a marked increase in the layers of cells in the alveoli with a tendency to papillomatous degeneration. The marked distention of the ducts by secretion is evident. There can be no doubt that this tumor developed greater unusual activities than previously observed in many hundreds of transplantations. Tissue from this tumor was autoimplanted into the same host and the injection of theelin continued for thirty-seven days, when

TABLE III. PERIOD OF TREATMENT: 163-368 DAYS

	AGE: 160 DAYS (ALL MALES)		AGE: 300 DAYS (ALL MALES)	
	CONTROLS	THEELIN TREATED	CONTROLS	THEELIN TREATED
39 animals	8	12	7	12
Per cent takes	63	50	43	42
Daily tumor gain	+0.06	+0.02	+0.02	+0.05
Daily body weight change	+0.30	+0.20	+0.15	-0.09
Total Int. units theelin		2,300-5,200		2,300-5,200
Autopsy weights of:				
Testes	2.45	2.45	2.06	1.55
Pituitary	0.015	0.014	0.014	0.013
Adrenals	0.073	0.050	0.055	0.172
Thyroid	0.059	0.052	0.044	0.045
Spleen	1.28	1.14	1.12	1.21
Liver	19.29	15.06	16.00	12.81
Kidneys	3.08	2.75	2.99	3.08
Bi-weekly injections: 50 I.U.				

the animal unexpectedly died. The study of the autoimplantation revealed that the glandular component of the tumor had become predominant over the connective tissue element, orderly arrangement of glandular structures disappeared, and the tumor was permeated with long strands and masses of cells of irregular size, highly suggestive of a malignant state (Fig. 12). However, the normal mammary tissue of the host did not show any of these changes. In fact, none of the normal mammary tissue of any of the injected animals showed a greater response to theelin than would be expected from prolonged administration of the hormone. Ducts and tubules showed a fair amount of cellular activity but in only two animals was the proliferation sufficient to approach the Schimmelbusch type. Alveoli showed some abortive attempts at the formation of lobules. Fibrosis was not significantly increased. It therefore can be stated that the injection of theelin in the amounts

indicated did not create any unpredictable changes in the normal mammary tissue of male rats of our strain.*

We concluded that while estrogen ordinarily did not influence the behavior of this mammary tumor any differently than in the previous experiment, the occurrence of an unusual hyperplasia with malignant tendencies in a tumor implanted in a younger animal might be of sig-

Fig. 9.

Fig. 10.

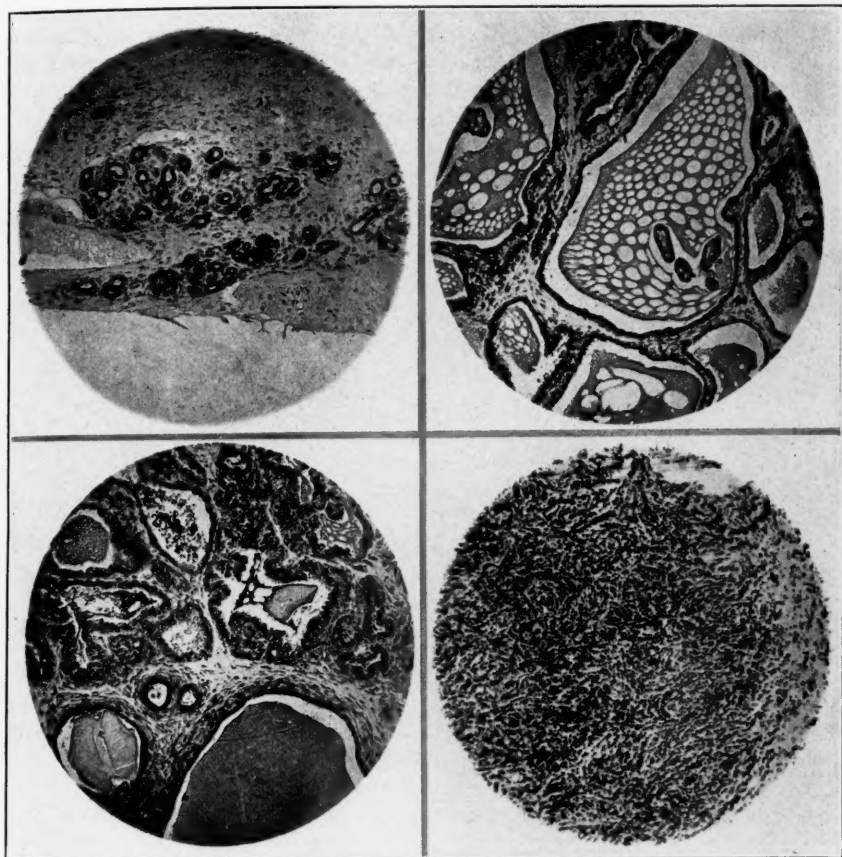


Fig. 11.

Fig. 12.

Fig. 9.—Male control of third experiment. Adenofibroma with groups of small glands without secretion.

Fig. 10.—160-day theelin treated male of Experiment 3. Adenofibroma showing unusual hyperplastic tendencies, densely packed with ducts and glands. Demonstration of tremendous ductile proliferation.

Fig. 11.—Another area of tumor of Fig. 10, showing massive areas of alveoli proliferation with considerable secretion.

Fig. 12.—Autoimplantation of tumor of Figs. 10 and 11. Demonstration of predominance of glandular components and loss of organization, suggestive of a carcinoid state.

nificance. We are now repeating this experiment with a larger group of animals and with larger doses of the hormone, using the oily solution instead of the aqueous substance.

*A detailed cytologic study of the mammary tissue will be reported elsewhere by Dr. N. J. Howard.

Autoimplants made in 15 animals of this experiment and treated with the same amount of theelin failed to yield further information. The tumors, instead of tending toward the cellular types, produced marked hyalinization. Seven animals which previously had failed to grow tumors were implanted with another rapidly growing adenofibroma, which also failed to grow. These animals, as well as the autoimplanted group, were given 50 units of theelin bi-weekly for 70 days, the total period of treatment covering 233 to 438 days, or nearly half the life span of a rat.

Being curious as to what would happen to tumor tissue from a theelin-treated male if transplanted into females and the theelin injections continued, we implanted tissue from a rapidly growing fibroma giving in-

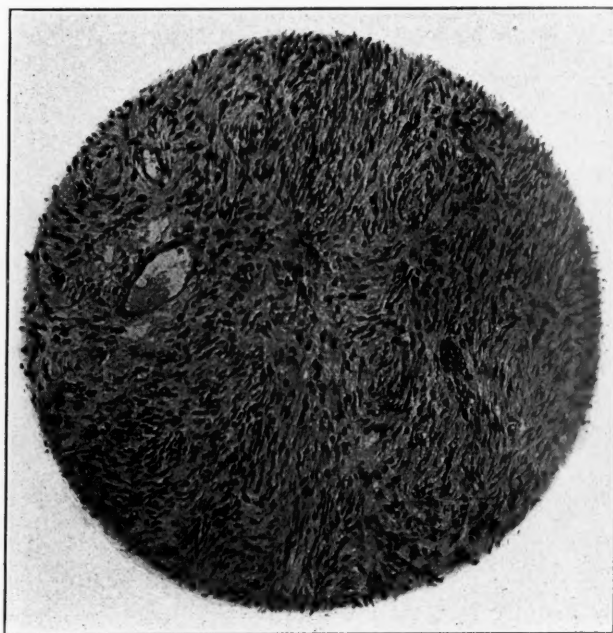


Fig. 13.—Theelin treated male of Experiment 3. Donor to Experiment 4. Very cellular fibroma with indications of sarcomatous tendencies.

dication of sarcomatous tendencies from Experiment 3 into 24 females and 12 males (Fig. 13). Twelve of the females were used as controls. The remainder were treated bi-weekly with 50 I.U. of theelin for 20 weeks. This tissue grew in about 75 per cent of all animals, and there was no essential difference between controls and injected animals (see Table IV). The implanted tumor was of a very cellular type, such as frequently preceded sarcomatous degeneration in subsequent transplantations. However, it contained many mast cells, and we are under the impression that when these cells are present sarcomatous degeneration will not develop readily. No unusual growth behavior was noticed. The growth rate was ordinary, and there were no further connective

TABLE IV. PERIOD OF TREATMENT: 139 DAYS

	CONTROL FEMALES	THEELIN TREATED FEMALES	THEELIN TREATED MALES
Age: 143-190 days			
36 animals	12	12	12
Per cent takes	83	58	75
Daily tumor gain	+0.12	+0.05	+0.13
Daily body weight change	+0.24	+0.23	+0.45
Total amount theelin		2,000 I.U.	2,000 I.U.
Bi-weekly injections: 50 I.U.			

tissue changes suggestive of sarcomatous degeneration. This tumor, although showing cytologic changes of the sarcomatoid type when exposed to long-continued injections of estrogen, did not degenerate into sarcoma.

DISCUSSION

The carcinogenic potentiality of the sex hormones is apparently extremely variable. Estrogen appears to possess this particular quality to a greater degree than other sex hormones. However, this quality seems to be strictly limited by certain biologic circumstances. There can be no doubt that estrogen plays some rôle in the production of a cancerous state of mammary, and occasionally of uterine, tissue of *mice susceptible to cancer*. It is equally important that little or none of this quality is shown in mice refractory to cancer, and it is further important that other rodents, particularly the rat, show far less susceptibility to this hormone than mice; and larger animals, as far as is known, remain entirely unaffected. We may therefore correctly assume that the carcinogenic potentialities of estrogen are limited by species differentials and probably by organ differentials and individuality characteristics. It seems likely that only tissues hereditarily prepared for unlimited hyperplasia can respond to the estrogenic impulse, and then, only under certain definite conditions. The mechanism of the hereditary transmission of this factor is still in dispute. Slye assumes that it follows the Mendelian rule, while Little considers it an extrachromosomal process. Whatever this mechanism may be, it is subject to the action of another factor yet unknown, which permits estrogen to change unlimited hyperplasia into uncontrolled tissue growth, or cancer. Probably the rôle played by estrogen is somewhat of the nature of that played by the nematode in Fiebigger's experiments, which prove that carcinoma of the stomach of the rat can be produced only if the right kind of nematode is fed to a particular cockroach, in turn fed to a particular kind of rat. If any of the factors were disturbed no carcinoma developed, and with all factors equal, carcinoma could be produced *only* in the stomach.

In our own experiments, some of this is illustrated. Both the transplanted and the normal mammary tissue are known to possess the ability for hyperplasia and a capacity for malignant degeneration of connective tissue structures. Although both tissues responded well to hormonal stimulation, their behavior was not influenced by the amount of estrogen administered or the length of treatment except in one instance, when a

tumor developed a carcinoid tendency. Therefore, a susceptible substratum existed only in *this* tumor, while neither the tumor mates nor the normal mammary glands of the tumor hosts showed signs of this characteristic. We expect it to be said that the dosage used by us was insufficient and that an aqueous preparation might act differently from an oily preparation. Granting the merit of this objection, we still consider the dosage not only adequate but excessive for the size of the animal used in these experiments, since it depressed the normal body weight gain. It is our opinion that the employment of larger doses would produce results not comparable with ordinary biologic occurrences. The important information sought is the response of functionally susceptible organs to long-continued administration of sex hormones in doses comparable with those used in clinical medicine. This, to us, is far more significant than the happenings following immense doses of sex hormones used in experimental studies.

Although we believe that the carcinogenic importance of estrogen is strictly limited by biologic conditions to certain tissues in certain species of mammalia, we feel that this evidence is still not sufficient to warrant the abandonment of caution in the use of large doses of this hormone in clinical practice. We have no knowledge of the latent effects of estrogenic hormones in higher mammalia, and until we do, vigilance is in order.

CONCLUSIONS

1. Transplantable mammary adenofibromas known to possess malignant potentialities were refractory to the influence of estrogen with the exception of one tumor, in which a carcinoid state occurred.

2. Estrogen did not prevent the loss of glandular tissue in mammary adenofibromas known to do so in the process of continued transplantation.

3. Tumors known to undergo sarcomatous changes did not show an increased sarcomatous tendency when exposed to continued estrogen administration.

4. Various dosages of estrogen administered to rats of different ages over long periods of time did not produce breast tissue changes beyond those expected for long estrogen stimulation.

The technical services of Mr. Pierre Lassagues and Mr. L. M. R. Wulff are gratefully acknowledged.

REFERENCES

- (1) Ancl, P., and Bouin, P.: *J. de physiol. et de path. gén.* 13: 31, 1911.
- (2) Bischoff, Fritz, and Maxwell, L. C.: *Am. J. Cancer* 27: 87, 1936. (3) Bonser, G. M.: *J. Path. & Bact.* 41: 217, 1935. (4) Burrows, H.: *Am. J. Cancer* 23: 490, 1935; *Ibid.* 24: 613, 1935. (5) Butenandt, A.: *Naturwissenschaften* 17: 879, 1929. (6) Cori, C. F.: *J. Exper. Med.* 45: 983, 1927. (7) Cramer, William, and Horning, E. S.: *Lancet* 230: 247, 1936. (8) Dingemans, E., Freud, J., de Jongh, S. E., and Laqueur, E.: *Arch. f. Gynäk.* 141: 225, 1930. (9) Doisy, E. A., Veler, C. D., and Thayer, S.: *Am. J. Physiol.* 90: 329, 1929. (10) Emge, L. A.: *Arch. Path.* 26: 429, 1938. (11) Emge, L. A., and Murphy, K. M.: *AM. J. OBST. & GYNEC.* 32: 593, 1936; *Proc. Soc. Exper. Biol. & Med.* 37: 620, 1938. (12) Emge, L. A., Murphy, K. M., and Schilling, W.: *Proc. Soc. Exper. Biol. & Med.* 38: 21, 1938. (13) Engel, P.: *Ztschr. f. Krebsforsch.* 34: 658, 1931. (14) Engle, E. T., and Smith, P. E.: *Anat. Record* 61: 471, 1935. (15) Evans, H. M., and Simpson, M. E.: *Proc. Soc. Exper. Biol. & Med.* 26: 597, 1929. (16) Frank,

- R. T., Goldberger, M. A., Salmon, N. J., and Friedman, R.: *Proc. Soc. Exper. Biol. & Med.* 32: 1665, 1935. (17) Gardner, W. N., Allen, E., Smith, G. M., and Strong, L. C.: *J. A. M. A.* 110: 1182, 1938; *Arch. Path.* 21: 265, 1936; *J. A. M. A.* 107: 656, 1936. (18) Heiman, J., and Krehbiel, O. F.: *Am. J. Cancer* 27: 450, 1936. (19) Hisaw, F. L., and Lendrum, F. C.: *Endocrinology* 20: 228, 1936. (20) Howard, N. J.: *Proc. Soc. Exper. Biol. & Med.* 34: 732, 1936. (21) Lacassagne, A.: *Compt. rend. Acad. d. se.* 195: 630, 1932; *Am. J. Cancer* 27: 217, 1936; *Ibid.* 28: 735, 1936. (22) Laqueur, E., de Jongh, S. E., and Tausk, M.: *Deutsche med. Wehnschr.* 53: 867, 1927. (23) Lathrop, A. E. C., and Loeb, L.: *J. Cancer Research* 1: 1, 1916. (24) Lewis, D., and Geschickter, C. F.: *Ann. Surg.* 104: 787, 1936. (25) Loeb, Leo: *J. A. M. A.* 104: 1597, 1935. (26) Loeb, Leo, Burns, E. L., Suntzeff, V., and Moskop, M.: *Proc. Soc. Exper. Biol. & Med.* 1: 320, 1937; *Canad. M. A. J.* 35: 117, 1936. (27) Loewe, S., Raudenbusch, W., and Voss, H. E.: *Biochem. Ztschr.* 249: 443, 1932. (28) MacDonald, I. G.: *Surg. Gynec. Obst.* 63: 138, 1936. (29) Mazer, Charles, and Israel, S. Leon: *J. A. M. A.* 108: 163, 1937. (30) McEuen, C. L.: *Am. J. Cancer* 27: 91, 1936. (31) Mohs, F. C.: *Am. J. Cancer* 29: 356, 1937. (32) Murphy, J. B., and Sturm, E.: *J. Exper. Med.* 42: 155, 1925. (33) Murray, William S.: *J. Cancer Research* 12: 18, 1928. (34) Nelson, W. O., and Pfiffner, J. J.: *Proc. Soc. Exper. Biol. & Med.* 27: 863, 1930. (35) Overholser, M. D., and Allen, E.: *Proc. Soc. Exper. Biol. & Med.* 30: 1322, 1933. (36) Perry, Isabella H.: *Proc. Soc. Exper. Biol. & Med.* 35: 325, 1937. (37) Perry, Isabella H., and Ginzton, L. L.: *Am. J. Cancer* 29: 680, 1937. (38) Sauerbruch, F., and Knake, E.: *Ztschr. f. Krebsforsch.* 44: 223, 1936. (39) Schinzinger, F.: *Verhandl. d. deutsch. Gesellsch. f. Chir.* 18th Congr. p. 28, 1889. (40) Suntzeff, V., Burns, E. L., Moskop, Marian, and Loeb, Leo: *Am. J. Cancer* 32: 256, 1938. (41) Taylor, H. C., Jr.: *Am. J. Cancer* 27: 525, 1936. (42) Turner, C. W.: *Mo. Agric. Exper. Stat. Res. Bull.* p. 156, 1931. (43) Witherspoon, J. T.: *Am. J. Cancer* 24: 402, 1935; *AM. J. OBST. & GYNEC.* 31: 173, 1936.

DISCUSSION

DR. J. MASON HUNDLEY, JR., BALTIMORE, MD.—Dr. Emge's observations on the changes produced in the mammary gland by long-continued injections of estrogen present many interesting facts, the most interesting to me being the relation between carcinogenic and estrogenic substances, and especially whether or not the estrogens used in the human being are likely to produce malignancy. Stimulated by the pioneer work of Yamagiwa and Ichikawa in 1915, when they showed that long-continued applications of tar to the ear skin of rabbits produced cancerous changes in the tissues, there has accumulated much information concerning carcinogenesis. It has been shown by Kennaway and Cook that the compounds in coal tar responsible for the reproduction of cancer are various hydrocarbons, the most powerful being methyleholanthrene. According to Loeb they may initiate cancer formation without first causing local irritation. It has also been shown that these carcinogenic substances are related chemically to cholesterol, bile acids, ergosterol and especially to the male and female sex hormones, all of these including the carcinogenic substances containing the phenanthrene ring.

The relationship between the estrogens and carcinogenic substances is of great interest, especially in regard to the estrogenic potency of carcinogenic hydrocarbons and the possible carcinogenic activity of the estrogenic hormones. Loeb states that in comparing these two series of compounds one may conclude that there are substances which are both carcinogenic and estrogenic; that there are carcinogenic substances which are not estrogenic and that there are estrogenic substances which are not carcinogenic.

Observing the marked proliferative effect of epithelium initiated by the prolonged injection of estrogens, a study of the carcinogenic properties of these substances has been undertaken by many investigators. The major portion of this investigative work has been carried out on selected strains of mice which developed spontaneous adenocarcinoma of the breast in variable proportions, appearing in 100 per cent of cases in certain strains and not at all in others. This incidence of development applies to the female, for rarely does such a growth occur in the male breast.

Lacassagne, one of the leading workers in this field, has been able to produce adenocarcinoma of the mammary gland in the male mouse by prolonged injections of estrone. Following the course of treatment, the growth appeared in 100 per cent of animals, both male and female, between the third and tenth months, the growths developing in a strain of mice in which one might expect tumors in only 72 per cent, only in the female and at the average of one year. Thus it is shown that if an artificial development of the male breast equal to that of the female is produced, the incidence of carcinoma of this organ will be the same in both sexes. He states that this finding does not prove whether the important cause for the development of the cancer is an hereditary factor or if it is solely the stimulative action of the hormone. In order to solve this problem he used a strain of mice in which only 2 per cent of the females spontaneously developed mammary carcinoma, the estrone injections in the male being given weekly from shortly after the time of birth. After eight months, none of the surviving animals developed growths, while in a similar period almost all of the mice of the strain previously studied died of adenocarcinoma of the breast. However, beginning with the ninth month, malignant tumors of the breast appeared, until between the twelfth and eighteenth months all the mice of this strain died of malignant growths of the breast. Here is demonstrated the fact that carcinoma will develop in mice of low cancer strain but will be greatly retarded in its development. In a final incompleted experiment he injected estrone, under the same conditions, into mice in which spontaneous cancer of the breast had never been observed. In twenty of these animals which survived more than six months, neither male nor female developed a breast tumor. The results of these three experiments show that the two most important influences in the production of mammary adenocarcinoma in the mouse are the hereditary and the hormonal factors.

Even with the great accumulation of experimental data at hand, obtained mainly from work on the mouse, we have to my knowledge very little positive information as to the carcinogenic activity of estrogenic substances in the human being. Because of the experimental production of mammary carcinoma and carcinoid processes in the cervix and vagina, estrogenic therapy in the human being is looked upon by some as a possible factor in increasing the probability of cancer. Such deductions are illogical for various reasons, one of the most important being that of dosage and duration of treatment. In Lacassagne's experiments, estrone benzoate in huge doses, approximately 1/200,000 of the body weight of the mouse, was injected weekly, begun shortly after birth and carried on nearly throughout the life of the animal. A corresponding dosage in a patient weighing 132 pounds would be 0.3 gm. of crystalline estrin or 3,000,000 I. U. at one dose, begun early in childhood and continued for several years.

Cramer and Horning state in the summary of their work with estrin that "the carcinogenic changes here described were produced by the administration of estrin over a period representing a considerable fraction of the normal span of life of a mouse and corresponding in man to a period of seven to ten years, while the therapeutic administration of estrin preparations in man is, in skilled hands, limited to short periods of a few weeks or months. The development of mammary cancer described in this paper should not, therefore, be used as an argument against the therapeutic application of estrin preparations."

I believe that the majority of physicians are in accord with this above statement and that the therapeutic application of estrogenic substances in the human being has practically no carcinogenic properties.

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Dr. Emge has used transplantable adenofibromas and has observed their behavior when growing in a single pure strain of rats under various hormone conditions produced by injection. We have been working on a similar problem but have taken two contrasted strains of mice, one of a high tumor incidence and one of low incidence. In this way we have been able to observe the behavior of spontaneous tumors growing in animals of apparently different endocrine constitution.

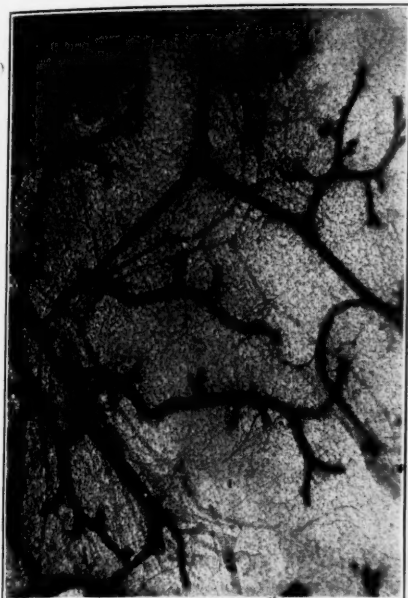


Fig. 1.

Fig. 1.—Mammary gland of untreated mouse of the cancer-resistant strain, aged 6 months.



Fig. 2.

Fig. 2.—Mammary gland of untreated mouse of cancer-susceptible strain, aged 6 months.



Fig. 3.

Fig. 3.—Mammary gland of mouse of cancer-resistant strain, aged 6 months, after four months' injections of estrone.

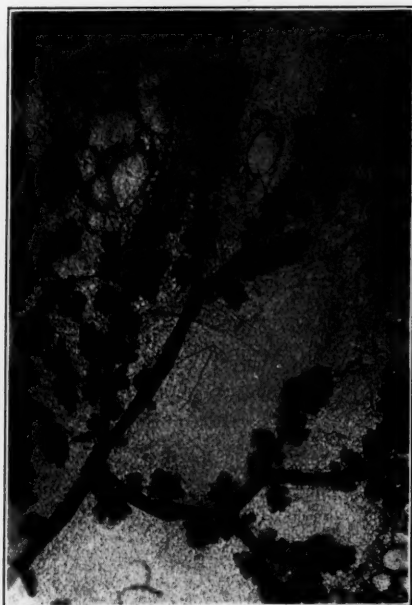


Fig. 4.

Fig. 4.—Mammary gland of mouse of cancer-susceptible strain, aged 6 months, after four months' injections of estrone.

Somewhat similar work has been performed by Lacassagne, Gardner, Burrows and others, but these workers have been interested especially in the relative incidence of cancer development. We on the other hand have been concerned with the precancerous changes, and especially their morphologic resemblance to the lesions occurring in the human disease known as chronic cystic mastitis.

These four gross mounts (Figs. 1 to 4) of mammary glands were all taken from animals six months of age. The first pair represent the contrasted morphology of the cancer-resistant and cancer-susceptible strains at the age of six months. You will note that the mammary gland of the resistant strain is much simpler and possesses almost no acini (Fig. 1), whereas the cancer-susceptible strain shows numerous lateral branches or alveoli (Fig. 2). These differences probably represent the earliest manifestation of the tendencies which lead to carcinoma in one animal and the freedom from it in the other.

The second point to be made is the effect of the injection of an estrogenic substance into these animals with different hereditary tendencies. This contrast is exhibited in the second pair of gross mounts. Both animals have been injected with an estrogenic substance for four months. One shows an enormous alveolar development (Fig. 4) while the other shows almost no response (Fig. 3). There is thus in addition to a structural difference developing spontaneously, a difference in the reactivity of the mammary glands to the injection of these hormones.

From these experiments which we have repeated with many animals, we can draw certain tentative conclusions. By all odds the most important factor in the development of mammary carcinoma in mice is this inherent constitutional factor. The addition of estrogenic substance simply emphasizes this difference. If one may make any inference as to the risk of giving estrogenic substances to women, one might expect that, if there is already a constitutional predisposition to mammary carcinoma in a certain woman, there may be a slight increase in the risk by giving her estrogenic therapy, whereas the woman who has no such constitutional predisposition is unaffected.

DR. EMGE (closing).—The nearest our experimentation comes to simulating the proliferative activities of mammary tissue in the human being is in the behavior of the ducts which suggests that type of hyperplasia commonly called Schimmelbusch's disease. In laboratory experimentation it has, however, been shown repeatedly that in certain strains and species of mammals, mammary tissue is incapable of exceeding certain limits of hyperplasia regardless of the amount of estrogenic hormone administered. This process must not be confused with the unlimited proliferation typical of malignancy.

It is to be expected that a constant stimulation by estrogen will create an exaggerated response in those tissues normally dependent upon this type of priming. It is important to realize that the extent of hyperplasia is predetermined and probably controlled by the same mechanism which governs cell growth. If this mechanism is defective, unusual hyperplasia may occur, provided the cells of the tissue affected possess the capacity for unusual hyperplasia. Somatic factors and hereditary susceptibility are therefore intimately related. Probably there are a number of other factors such as species, strain, and organ differentialities which further modify supernormal cell growth.

The studies presented here are preliminary to a more extensive investigation, the results of which we hope to report a year from now. Accepting that certain strains of lower mammals are hereditarily destined to grow mammary cancer, it is not surprising that an estrogenic hormone may accelerate this process. However, this does not prove that estrogenic hormones are carcinogenic agents in a broader sense, particularly in the human being.

OBSERVATIONS CONCERNING THE METABOLISM OF ESTROGENS IN WOMEN*

GEORGE VAN S. SMITH, M.D., AND O. WATKINS SMITH, PH.D.,
BROOKLINE, MASS.

(From the Fearing Research Laboratory, Free Hospital for Women, Brookline,
Mass.)

ONE of the characteristics of sex hormones which differentiates them from other internal secretions lies in the fact that they are excreted either in the same forms as presumably occur in the blood or in forms definitely recognizable as metabolic products. Quantitating these factors in the urine, even with still inadequate methods of extraction and with only approximately correct bio-assay, is gradually yielding more information regarding normal and pathologic situations.

INTRODUCTION

The metabolism of estrogenic hormones by women first engaged our attention when we noted that their oral administration resulted in detectable (with the methods then available) increased urinary excretion only during the luteal phase of the cycle.¹ A role of progestin in the excretion of estrogens had previously been indicated by experiments with rabbits, namely, that injected estrone could be recovered in fair quantities in the urine of ovariectomized does only if progestin were simultaneously administered.²

With improved methods quantitation of total urinary estrogen throughout normal menstrual cycles demonstrated a peak of excretion early in the period of luteal activity with low levels just before menstruation and during follicle ripening.³ The most conclusive evidence that this type of curve represents a normal ovulatory cycle is the fact that two women, studied before and during the month of conception, showed exactly this curve of excretion to the twenty-fifth day.³ The drop in estrogen before flow is in keeping with the "estrin-withdrawal" theory of menstruation.

In four instances (two of which are shown in Chart 1) thus far, curves of total urinary estrogen lacked the characteristic intermenstrual peak and, furthermore, rose before the onset of bleeding. They are assumed to represent anovulatory cycles. The high level at the start of flow argues against the "estrin-withdrawal" theory.

*Presented at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by a grant from the Committee on Research in Endocrinology of the National Research Council.

It seemed possible that quantitation of the two estrogens which have been identified in human urine, namely, estrone and estriol, might yield more information than the determination of total estrogen. Consequently, a cycle was followed in which the total estrogen was separated into estrone and estriol fractions, which were then assayed.⁴ It was noted that estriol reached its highest level during the luteal phase and practically disappeared at menstruation, at which time nearly all the estrogenic potency of the urine was in the estrone fraction.

This association of increased excretion of estriol with luteal activity, and vice versa, had been anticipated because of Pincus' and Zahl's

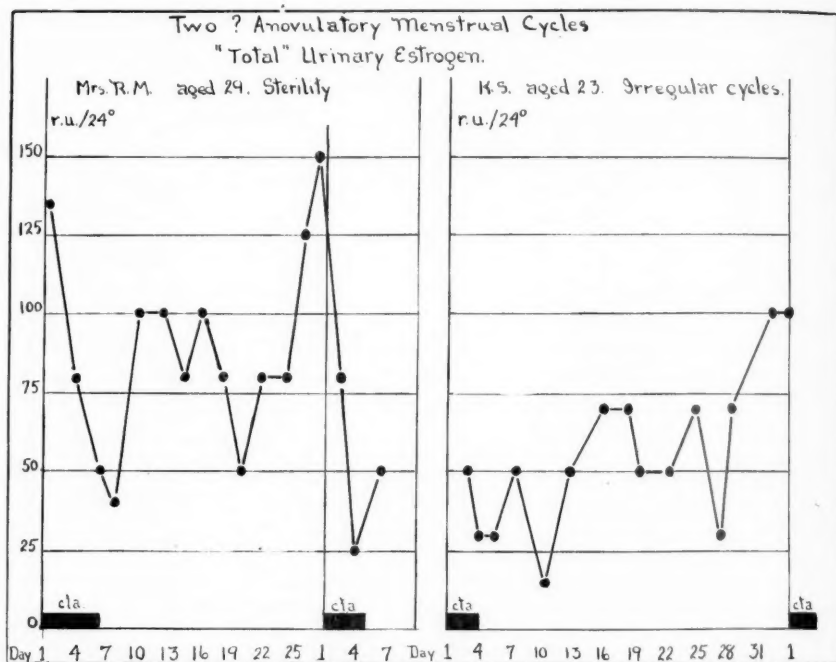


Chart 1.

experiments with rabbits^{5, 6} in which they had determined the urinary excretion of estrone and estriol under various conditions after the injection of known amounts of estrone, estriol, and estradiol. Their findings indicate: (1) that estradiol (which, according to MacCorquodale, Thayer and Doisy,⁷ is in all likelihood the primary ovarian estrogen) is converted into estrone by rabbits with ovaries and that this reaction is reversible—chemical evidence also demonstrates the reversible nature of the estradiol to estrone conversion;⁸ (2) that estrone is converted into estriol when the uterus is present and under ovarian control, this conversion being irreversible and greatly facilitated by luteal secretion; and (3) that progestin partially protects these three estrogens against destruction, thus permitting both utilization and ex-

cretion, there probably being no renal threshold. Based on these observations, and our own, in women, the schematic representation of the metabolism of the estrogens given in Chart 2 has been evolved.

Relatively high levels of estriol excretion, then, during what was presumably the luteal phase of the cycle suggest that in women, as in rabbits, excretion of estriol may be taken as a gauge of secretion of progestin. Thus would the marked drop in estriol two days before menstruation signify regression of the corpus luteum. This interpretation is strengthened by the work of Venning and Browne⁹ who find that pregnandiol glucuronide, the excretion product of progestin, disappears from the urine one to three days before the beginning of

Metabolism of the Estrogens

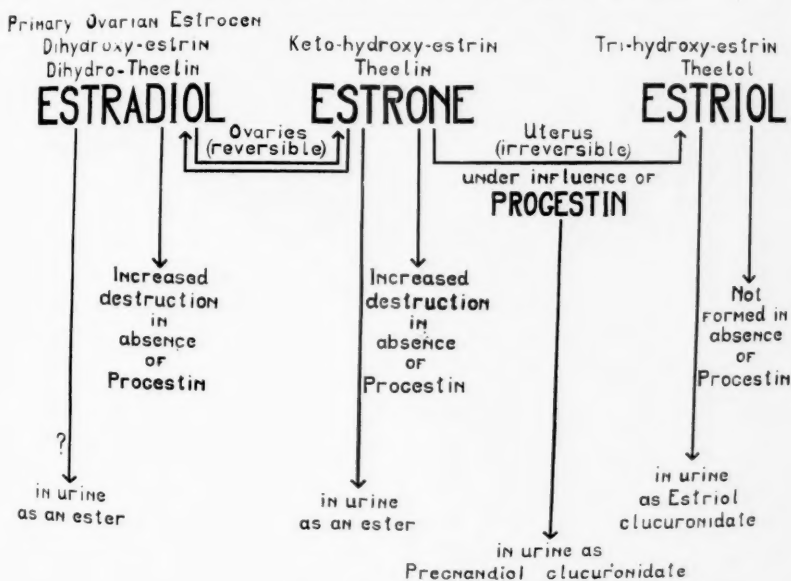


Chart 2.

flow. With the onset of menstruation there was a further drop in estriol and a rise in the potency of the estrone portion, so that the ratio of estrone to estriol during the first two days was much higher than at any other time in the cycle. This observation has been confirmed in another normally menstruating woman (*v.i.*) and is sufficiently definite to suggest that something more than a withdrawal phenomenon may be concerned in the initiation of normal menstruation, just as the increase in estrogen excretion at the time of anovulatory flow may be construed as reflecting some positive influence. In measuring "total" estrogen in normal cycles, this estrone rise would be masked by the drop in estriol.

Throughout a normal pregnancy also were urinary estrone and estriol determined.⁴ From the time of the second missed catamenia

excretion of estriol increased at a more rapid rate than that of estrone, resulting in constantly higher ratios of estriol to estrone. In the urine of pregnancy, Browne, Henry and Venning have quantitated pregnandiol glucuronide¹⁰ and have found a constant increase of this excretion product of progestin with advancing gestation, this indicating progressively greater secretion of progestin. Here again, as in the menstrual cycle, urinary estriol is apparently a gauge of the amount of progestin. Preceding delivery estriol excretion dropped off markedly, and there was a concurrent augmentation of the potency of the estrone fraction, which comparison of colorimetric assay⁴ with bio-assay indicated was due to some estrogen other than estrone. These findings, analogous to those at menstruation, suggest that in the initiation of labor, as in the initiation of menstruation, progestin deficiency in the presence of estrogen production may result in a changed metabolism of estrogens and the consequent action of a positive precipitating factor. In the determination of "total" estrogen at the time of delivery, any rise in the estrone fraction would be completely marked by the drop in estriol. In the paper⁴ in which the above material was first reported we predicated that the hypothetical positive factor might actually be estrone. Further consideration of the known facts about endometrial bleeding and delivery, however, and the investigations to be presented below lead us to believe that the rise in the estrogenic potency of the estrone fraction at the time of these processes may be an indication of the action of a positive factor but not "the positive factor" itself.

FURTHER OBSERVATIONS CONCERNING THE METABOLISM OF ESTROGENS

At this point it is pertinent to point out that, although estrone and estriol have been obtained in crystalline form from the urine of pregnant women, there is no proof that they are the only estrogens excreted during pregnancy. Furthermore, the urinary estrogens of the nonpregnant have not been isolated and identified, but, on the basis of consistent findings, we have assumed them to be estrone and estriol. In order to test further the method of hydrolysis (Smith and Smith) and separation (Cohen and Marrian) used in these investigations, we have added pure estrone, estriol, and estradiol* in varying proportions to 100 to 700 c.c. amounts of urine from nonpregnant women, the titration values of which were simultaneously determined. Estrone, due to its ketonic nature, combines with semicarbazide hydrochloride to form a biologically inert semicarbazone.¹¹ Neither estriol nor estradiol has this property. By semicarbazide treatment, then, it can be discovered whether or not any estrone is present in estriol fractions, or any nonketonic estrogen in estrone fractions. These recovery experiments have demonstrated that crystalline estrone, estriol, and

*We wish to express our gratitude to the Schering Corporation, which, through Dr. Gregory Stragnell and Dr. Erwin Schwenk, has supplied us not only with the above substances but with large quantities of specially prepared proluton (progesterone) and progynon-B (estradiol benzoate) for clinical trials.

estradiol are not destroyed by the hydrolysis, that separation of estrone from estriol is complete and that estradiol is entirely taken over into the estrone fraction.* If these three should be the only estrogens elaborated by women, it may be concluded that the potency of estriol fractions is entirely due to estriol, whereas the potency of estrone fractions may be due to estrone and/or any estradiol that escapes into the urine prior to conversion or destruction. Since estradiol is 10 times as strong estrogenically as estrone, even minute amounts of it would significantly raise the activity of estrone fractions. As mentioned above, comparison of colorimetric with bio-assay⁴ gave evidence for the presence of some estrogen much more active than estrone in the urine of late pregnancy. Treatment by semicarbazide of the estrone fractions of urines from both pregnant and nonpregnant women has given further evidence for the excretion of some estrogen other than estrone and estriol. It seems reasonable that this third factor is estradiol, but, lacking direct proof, we shall refer to it as "x" estrogen.

NORMAL MENSTRUAL CYCLE

We have not yet been able to perform estrone-estriol separations together with semicarbazide treatment of the estrone fractions throughout a normal menstrual cycle. On four specimens from one individual, however (Chart 3), this procedure has been followed. Based on a calendar record, the individual's cycles never vary from twenty-eight days by more than twenty-four hours. The specimens were collected as follows: one during the follicular phase, one during the luteal phase, the third for the forty-eight hours preceding menstruation, and the last for the first two days of flow. The findings agree with those already published and go further in showing that a large proportion of the potency of the estrone fraction is accountable to "x" estrogen. If the results are expressed in micrograms rather than in rat units and the "x" estrogen assumed to be estradiol, it is evident that this substance is excreted actually in very small amounts by weight. Its presence in all these specimens would signify that at no time in the cycle is the estradiol to estrone to estriol conversion complete. Most conversion, judging by the percentage of estriol excretion, appears to take place during the second half of the cycle, as would be expected. During the last two days, despite low total estrogen, the percentage of estriol remains unchanged, indicating that a metabolic balance between estrogen and progestin is still being maintained.

*All values recorded in this paper were obtained by bio-assay performed according to the technique previously described.⁴ The recovery experiments reported in this earlier communication were done with 100 c.c. amounts of urine. The extraction of larger volumes apparently introduces a greater chance for loss (never more than 25 per cent). In the analysis of urines from pregnancy we routinely extract 100 c.c. per liter of the twenty-four-hour volume. It is usually necessary to extract the whole of a forty-eight-hour specimen from the nonpregnant to obtain sufficient estrogenic material for accurate bio-assay. However, since approximately equal volumes of different specimens are used, the results should be comparable despite the unavoidable loss.

With the beginning of flow, however, estriol reaches its lowest level and there is a threefold increase of "x" estrogen, estrone itself being entirely absent. We believe this shift in excretion of estrogen at menstruation to signify the growth of a new ovarian follicle (a process known normally to follow upon reduced activity of the corpus luteum) with increased production of estradiol. Progesterin being deficient for the amount of secreted estrogen, there is but little conversion to estriol. A failure in conversion would result in a higher concentration of estrone and estradiol, both of which factors are rapidly destroyed in the absence of progesterin. In fact, whatever estrone is

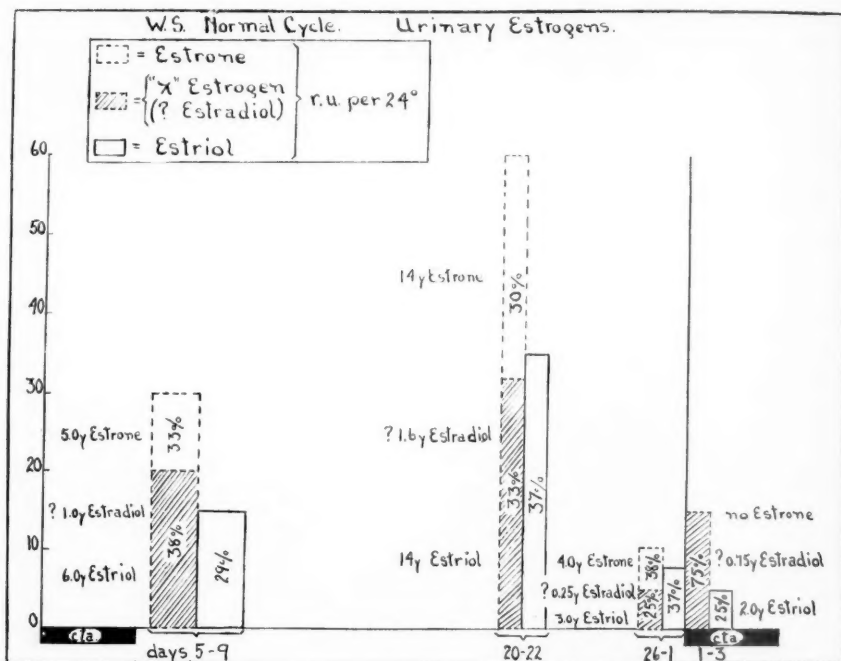


Chart 3.

Erratum: Days 5 through 9 of normal cycle: Estrone should be 22.5 per cent; "x" estrogen should be 44.5 per cent; estriol should be 33.0 per cent.

not converted to estriol or back to estradiol is so rapidly destroyed that none can be detected in the urine. We are led to wonder whether concentration in the endometrium of nonestrogenic, possibly toxic, sterols resulting from estrogen destruction may not be concerned in the local vascular phenomena which are involved in menstruation. By this thesis both ovulatory and anovulatory flow could be explained, viz., production of estrogen in the face of deficient or absent progesterin with a resultant shift in the metabolic chain of events, giving breakdown products of estrone and estradiol instead of estriol, and consequent flow, providing the endometrium is sufficiently proliferated.

DYSFUNCTIONAL FLOWING

Quantitation of the estrogens in the urines from a patient* with dysfunctional flowing (Chart 4) has confirmed the above data and lent more plausibility to the ideas derived therefrom. This patient is a typical refractory case, aged 23, who has been under observation and various conservative treatments for four years. Frequent biopsies have consistently revealed a "Swiss cheese" endometrium. She gives a history of irregular flowing since puberty at the age of fifteen. Bouts of prolonged and excessive flowing have been interspersed with periods both of constant dark discharge and of amenorrhea lasting

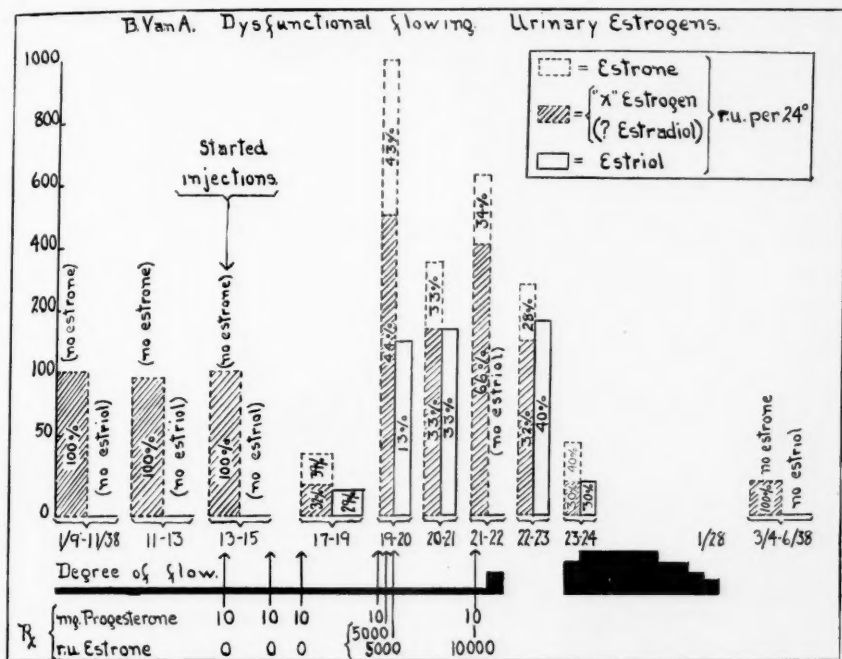


Chart 4.

three to four months. One such span of amenorrhea followed resection of a 3 cm. cyst of the left ovary nearly four years ago. At the time this study was begun she had had constant dark discharge for four months with occasional short spells of bright flow with clots. She was put to bed and placed on constant urinary drainage. For the four days preceding injections the urine contained comparatively high estrogenic activity, all accountable to "x" estrogen (estradiol ?). This signifies to us such rapid secretion that goodly amounts were being spilled over into the urine. No estriol was detected, indicating, as would be expected in this patient, a uterus completely lacking luteal control. Lack of progestin involves increased destruction as

*We are indebted to Dr. John Rock for essential cooperation in the study of this case.

well as failure of conversion. In fact, if there was any conversion to estrone, this substance was being so rapidly destroyed that none escaped into the urine.

The administration of progesterone* resulted (after the third injection) in the excretion of appreciable amounts of estrone and estriol, this constituting our first post hoc evidence for the role played by progestin in the conversion to estriol. The fact that estrone also appeared in the urine indicates, first, the effect of estriol formation in carrying the reversible estradiol to estrone reaction to the right, and second, the protective action of progesterone against estrone destruction, thus allowing excretion. Administration of progesterone also resulted in a 50 per cent decrease in the total estrogenic potency of the urine. However, if "x" estrogen is assumed to be estradiol and the urinary estrogens are expressed in micrograms rather than rat units, the excretion before progestin therapy amounts to only five micrograms and afterward to a total of 17 micrograms (10 micrograms estrone, 1 microgram estradiol and 6 micrograms estriol), indicating that conversion was accompanied by decreased destruction. This medication had no effect on the patient's flowing.

On the tenth day of the experiment (Jan. 19 and 20, 1938), injection of 10 mg. of progesterone was followed in the course of the next six hours by the injection, in two doses, of a total of 50,000 I. U. of estrone.† There was recovered on this and the following day about 16 per cent of the injected material in terms of rat units, but on differential analysis only 42 per cent of this consisted of estrone, the hormone administered, while 38 per cent was accountable to "x" estrogen and 20 per cent to estriol. Not knowing how much of the injected estrogen would have been recovered had the patient not received progesterone, it is impossible to state how much protection of estrogen progesterone afforded in this instance, although it is a fair assumption that even less total estrogen would have been recovered without progesterone. The presence of estriol means conversion. A good proportion of the estrone was also obviously changed to "x" estrogen (estradiol?). In other words, the indications are that, although sufficient progesterone was given to render partial protection against destruction of the estrogens and to cause some estrone to estriol conversion, the amount of administered estrone was more than could be efficiently taken care of by the progestin activity, since urinary studies gave evidence for considerable destruction as well as reversal of the estradiol to estrone reaction. There was no alteration in the amount of flow.

On the twelfth day (Jan. 21 and 22, 1938), 10 mg. of progesterone and 50,000 I.U. of estrone were injected together. Urinalysis for the twenty-four hours failed to reveal any estriol. Apparently the large

*Proluton, Schering Corporation.

†Theelin, kindly made up for us by Parke, Davis & Co., through the courtesy of Dr. E. A. Sharp. 50,000 I. U. \approx 10,000 R. U. by our assay.

doses of estrone had temporarily prevented the progesterone from influencing the uterus, just as Allen¹² demonstrated in rabbits and Zuckerman¹³ in monkeys, thereby inhibiting conversion to estriol. Failure of conversion would necessarily (according to our theory) involve increased destruction, and this was clearly the case, since considerably less total estrogen was recovered following this injection of 50,000 I. U. than during the twenty-four hours after the previous similar treatment. It seems significant that the patient had a twelve-hour spell of bright flow during this time of rapid destruction. Forty per cent of the estrogenic activity of the next twenty-four-hour specimen (Jan. 22 and 23, 1938) was due to estriol, the interpretation being that, through destruction and excretion, there was sufficient decrease of estrogen to allow progesterone to act. Flowing ceased completely during this time. On the fourteenth day (Jan. 23, 1938), two days after the last injection, one of the severest bouts of flowing occurred that the patient had ever experienced, lasted three days, then diminished and stopped completely by Jan. 28, 1938. The specimen collected during the first twenty-four hours of excessive bleeding was similar in amount and kind of estrogen to that preceding the estrone injections. Since it is apparent that very large amounts of estrone were being destroyed between the nineteenth and twenty-third of January, it is tempting to postulate that the ensuing flow was due to a greater concentration of breakdown products involving more endometrium.

There has since been no "show" whatsoever (as of May 25) and a twenty-four-hour specimen early in March was low in total estrogenic potency, all of the activity present being accountable to "x" estrogen (estradiol?). We would conclude that this patient's ovaries are still completely lacking in luteal activity, and that bleeding will begin again as soon as the endometrium shall have sufficiently proliferated to respond to whatever effect is associated with a progestin-deficient metabolism of the estrogens. It is impossible to reconcile the findings in this case with the "estrin-deprivation" theory of menstruation, since, during the control period, the patient was bleeding when the urinary excretion of estrogen was at a constant level five times as high as was found during a nonbleeding phase.

TOXEMIA OF LATE PREGNANCY*

In a normal pregnancy (*v.s.*) estriol excretion appeared to reflect progestin secretion. To confirm this and to discover any abnormality in the level of progestin in patients with late pregnancy toxemia, a total of 88 specimens of urine from 18 pregnant women have thus far been assayed for estrone and estriol. Pregnanediol has also been measured¹⁴ in 64 of these. Seven of the patients had normal pregnancies, 9 had late pregnancy toxemia and 2 eclampsia. The results agree that secretion of progestin, based on urinary pregnanediol, is paral-

*We wish to acknowledge with gratitude the cooperation of Drs. Elliott P. Joslin, Frederick C. Irving, Priscilla White and Samuel B. Kirkwood in these studies.

leled by the percentage of estriol in the urine. Furthermore, they indicate that a deficiency of progestin pertains at the time of the clinical manifestation of late pregnancy toxemia and eclampsia, the actual evidence being low urinary pregnandiol and estriol, as compared with normals, and a decreased ratio of estriol to the potency of the estrone fraction, due either to low estriol alone or to both low estriol and excessive activity in the estrone fraction. Weil¹⁵ has also reported that the values for urinary pregnandiol in cases of toxemia of pregnancy are below those for normal pregnancy.

In a limited number of specimens so far the potency of the estrone fractions has been measured before and after treatment with semi-

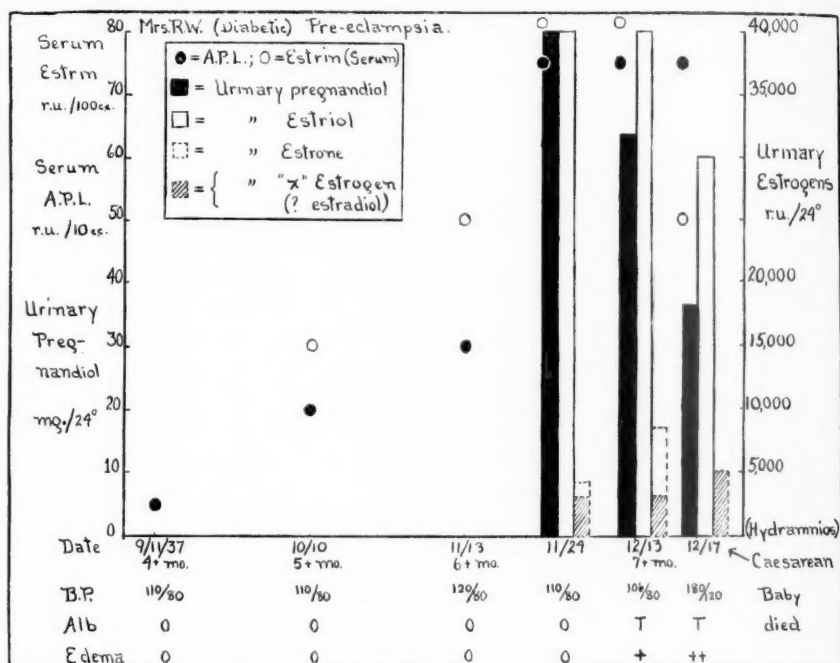


Chart 5.

carbazide. One patient, a diabetic (Chart 5), was studied prior to the development of pre-eclampsia. The first urine was collected because of the abnormal rise in serum anterior pituitary-like substance (prolan, anterior pituitary-like substance), which led us to anticipate trouble.¹⁶ Clinically the patient was still progressing through a normal gestation and the first values for pregnandiol, estrone, estriol, and "x" estrogen were within the limits of normal. Three weeks later another urine was obtained, the patient having developed some edema and albuminuria. Pregnan- diol had dropped; estriol had not risen. Estrone excretion, however, had increased and semicarbazide treatment revealed the augmen- tation to be due to estrone and not "x" estrogen. These analyses sig- nify to us increased elaboration of estrogens, as is normal with ad-

vancing pregnancy, but reduced conversion of estrone to estriol, which is consistent both with reduced progestin (based on urinary pregnandiol) and failure of a rise in estriol.

Four days later the patient's blood pressure suddenly went up and edema was more pronounced. Urinalysis revealed less pregnandiol and estriol and complete disappearance of estrone, the activity of the estrone fraction being accountable entirely to a rise in "x" estrogen. These shifts in excreted materials are quite comparable with those which occur at the time of menstruation and constitute evidence for an analogous situation, namely, production of estrogen in the face of a deficiency of progestin with resultant inadequate conversion and greater destruction. Is it possible that the vascular phenomena of pre-eclampsia may be precipitated by the same changes in estrogen metabolism that occur at menstruation? Again it is tempting to postulate that an increased concentration of estrogen breakdown products is concerned. "Toxemia" may be the correct term after all.

TOXEMIA OF LATE PREGNANCY TREATED BY ESTROGEN AND PROGESTERONE—PRELIMINARY REPORT

The employment of estrogen in late pregnancy toxemia was rationalized by the finding of low levels of estrogen and high anterior pituitary-like substance in the serum and urine of patients with this syndrome.*¹⁶ Since these two hormones seem to be mutually antagonistic (high anterior pituitary-like substance almost invariably being associated with low estrogen and vice versa), administration of estrogen appeared to be the logical way to re-establish a balance. We have in fact found, in six cases now, that injection of estrogen alone was followed by a lowered titer of anterior pituitary-like substance. Even massive doses, however, have failed to raise the level of serum estrogen. Our more recent investigations offer an explanation for this, namely, that these women were not secreting enough progestin to protect the additional estrogen against destruction. This consideration, strengthened by the finding of low urinary pregnandiol, makes therapy by estrogen *plus* progestin a more reasonable procedure to follow in the hope of re-establishing a normal hormonal balance in toxemia of late pregnancy.

A patient with severe pre-eclampsia in the seventh month was the first to receive a trial of this therapy. At the time neither pregnandiol nor "x" estrogen was being quantitated, but the anterior pituitary-like substance of both serum and urine was strikingly high and the urinary estrogens were low, there being, however, in the estrone fraction an abnormally large proportion of the estrogenic activity. Four days of treatment with a total of 25 mg. of progesterone† and 750,000 I. U. of estradiol benzoate‡ resulted in a shift of the anterior pituitary-like substance estrone and estriol toward normal. There was also a rise in serum

*Actually, to May, 1938, 70 out of 80 patients diagnosed as having pre-eclampsia and eclampsia, and studied by us, had this imbalance.

†Proluton.

‡Progynon-B, Schering Corporation.

estrogen. Clinically, however, no change for the better could be detected. It became necessary to stop therapeutic trials because of severe urticaria around the sites of injection. Three days later, coincident with a recurrence of high anterior pituitary-like substance, a decrease in urinary estriol and more activity in the estrone fraction (the changes in estrogens being of the same sort as described above [see "Introduction"]) in the urine of a patient at the time of normal delivery), mild spontaneous labor started, the membranes were ruptured and twins delivered. Four convulsions occurred during the subsequent sixteen hours. Both mother and infants were well six weeks later.

This case demonstrated two important points: first, that therapy with progesterone and estrogen, with the kinds and amounts administered, had no immediate or dramatic effect upon the severe pre-eclampsia; second, that the medication not only did reduce anterior pituitary-like substance but raised serum estrogen and changed the urinary estrogens in the direction of a normal balance. It is only fair to state, however, that conclusions based on the data derived from urinary studies in a case of this sort can be only approximately correct, since there was a considerable element of error introduced by the presence of much albumin, which renders extraction and separation less satisfactory.

Another patient, a diabetic, who had had pre-eclampsia with her previous pregnancy and had delivered a macerated fetus (Mrs. Wh., Charts 5 to 8),¹⁶ was treated at the onset of mild toxemia (albumin, slight trace; edema, +) at seven and one-half months, when pregnandiol had dropped 50 per cent and urinary estrogen was extremely low. For the previous four weeks serum anterior pituitary-like substance had been found to be increasing. Over a period of two weeks she received 140 mg. of progesterone and 1,650,000 I. U. of estradiol benzoate. During this time her blood pressure fluctuated from 120/80 to 150/110 and albumin from nothing to a trace. There was a negligible amount of edema. At the eighth month she was delivered. Mother and infant did well.

With the injections anterior pituitary-like substance fell to normal (100 R.U./100 c.c. serum), serum estrin rose and both pregnandiol and estriol in the urine increased markedly, the potency of the estrone fraction remaining down. In other words, the balance was thrown well toward normal.

The question that cannot be answered in this instance is whether or not medication, administered at the onset of early manifestations, warded off a more serious situation, even if it did not bring about a complete return to normal clinically. (On the day before delivery the blood pressure was 120/80, there was the slightest possible trace of albumin and edema was barely detectable.)

A third "pre-eclamptic," a primipara, aged 28 years, who, over a period of nine days, received 170 mg. of progesterone and 2,550,000 I. U. of estradiol benzoate, showed no clinical change whatsoever and

had a spontaneous delivery late in the eighth month, four days after the last injection. In contrast with the others, however, the anterior pituitary-like substance of serum and urine on two occasions shortly before treatment was normal, as were also urinary pregnandiol, estriol, and estrone. This constitutes the tenth case that we have studied in which a clinical diagnosis of pre-eclampsia failed to be associated with the typical hormonal imbalance. In nine other cases, definitely diagnosed as nephritic, normal values for serum anterior pituitary-like substance were found. As Kellogg¹⁸ suggests, determination of anterior pituitary-like substance may find a place as a test for the presence or absence of true pre-eclampsia. Regardless of the diagnosis, one would expect no benefit from endocrine therapy in a situation with no demonstrable hormonal abnormality.

Three other patients, diabetics, have been treated similarly on the basis of raised serum anterior pituitary-like substance between the fifth and seventh months. None of them had developed any clinical evidence of toxemia at the time medication was begun, in the seventh month. The urinary studies are not finished and will be reported later in detail. All three patients progressed through uneventful pregnancies to within three weeks of term and were then delivered of vigorous, well babies. This type of therapy, given early, would seem to offer promise of clinical success.

The results of such preventive measures are difficult to evaluate. In the course of the last five years, however, we have assayed for anterior pituitary-like substance 520 serums from 164 women. There were no normal pregnancies among the 78 cases with high serum anterior pituitary-like substance. Moreover, of 28 women in whom an abnormal augmentation of serum anterior pituitary-like substance was discovered between the fifth and seventh months, 21 developed toxemia of varying degree four to six weeks later and the other seven had spontaneous premature deliveries. We are inclined to the opinion, therefore, that treatment was successful in the last three cases, although many more such outcomes will be required to constitute incontrovertible evidence.

It is difficult to understand why excessive anterior pituitary-like substance, a hormone whose characteristic property is its luteinizing effect, should be followed by a deficiency of progestin with the consequent shift in the metabolism of the estrogens. This apparent paradox calls for further study, and suggests that the high values for anterior pituitary-like substance in pre-eclampsia may possibly be due to some synergistic factor rather than excessive production of anterior pituitary-like substance itself. A pituitary synergist has been ruled out by previously reported tests on hypophysectomized rats.¹⁷ We still feel that this "prolan" abnormality is somehow involved in the primary etiology of pre-eclampsia, although the present investigation would indicate that the clinical manifestations are precipitated by a situation analogous to that at the time of menstruation, viz., a progestin-deficient metabolism of the estrogens.

DISCUSSION

In the interpretation of the data presented it has been theorized that a positive precipitating factor associated with a progestin-deficient metabolism of the estrogens may be responsible for both endometrial bleeding and late pregnancy toxemia. We realize that this hypothesis is not entirely justified on the basis of the actual findings. If total estrogen alone is considered, the data on normal cycles are entirely in keeping both with the progestin- and estrin-withdrawal theories of menstruation. However, in the cycles in which estrogen rose at the time of flow, and in the case of dysfunctional flowing in which five times as much total estrogen was being excreted at the time of bleeding as was found in the nonbleeding phase, it would seem that estrin withdrawal cannot apply. For this reason and because of the evidence for a striking change in estrogen metabolism at the time of both types of flow from that found in the intermenstrual period of a normal cycle, it is tempting to postulate that some factor associated with or produced by this changed metabolism may actually be the direct cause of endometrial breakdown. Inasmuch as the partition of the urinary estrogens when bleeding occurs, and also in toxemia, is indicative of increased destruction, one is naturally led to theorize that breakdown products may be responsible.

Certain observations in connection with the production of experimental endometrial bleeding are difficult to reconcile with this hypothesis, e.g., the latent period and the inhibition of bleeding by maintaining a sufficiently high dose of estrogen.

Regardless of the interpretation of the results, it is evident that a marked change in the metabolism of estrogens takes place at the time of menstruation and at the appearance of clinical signs in late pregnancy toxemia. Furthermore, this change would not have been detected had we limited ourselves to the determination of "total" urinary estrogen.

SUMMARY AND CONCLUSIONS

Estrone and estriol have been quantitated (1) in 4 specimens of urine from a normally menstruating woman at crucial times in the cycle; (2) in 10 urines from a patient with dysfunctional flowing—during a control period, after progesterone and after progesterone and estrone; and (3) in 88 urines from 18 cases of late pregnancy, 7 normal, 9 toxemic, and 2 eclamptic.

An as yet unidentified ("x") estrogen, presumed to be estradiol, has also been quantitated in the specimens from the woman with normal catamenia, from the patient with dysfunctional flowing and from one of the patients with pre-eclampsia, who was studied before and after the appearance of signs.

Pregnanediol has been measured in 64 of the urines of pregnancy.

Physiologically the determinations, confirming and enlarging upon Pincus' studies with rabbits, indicate:

1. That estradiol is convertible into estrone and estrone into estradiol.
2. That progestin, acting through the uterus (probably the endometrium), brings about the conversion of estrone to estriol, thus carrying the estradiol to estrone reaction to the right. Accordingly, the distribution of the estrogens in the urine supplies an index of progestin activity.
3. That progestin partially protects the estrogens against destruction, thereby allowing greater utilization and excretion. The amount of estrogen in the urine represents the balance between production and destruction.
4. That deficiency of progestin, therefore, results in (1) reduced conversion of estrone to estriol, (2) thus causing the estradiol to estrone reaction to swing to the left, and (3) greater destruction of all estrogens.

Clinically the determinations indicate:

1. That endometrial bleeding is associated with both increased production and increased destruction of estrogen, which processes accompany a state of progestin deficiency, and that this situation is exaggerated in dysfunctional flowing.
2. That the manifestations of pre-eclampsia coincide with changes in the urinary values for pregnandiol, estrone, estriol, and estradiol which reflect a progestin-deficient metabolism of the estrogens.

It is postulated that the vascular phenomena which are responsible for endometrial flow and pre-eclampsia may be brought about by a toxic concentration of nonestrogenic breakdown products, resulting from destruction of the estrogens.

A preliminary report is included on the treatment of pre-eclampsia with large amounts of progesterone and estradiol benzoate. Thus far it appears that such therapy shifts the progestin-estrogen balance in the direction of normal and offers some promise of value, provided injections are started sufficiently early.

We are indebted to Miss Sara Schiller for valuable technical assistance in this investigation.

REFERENCES

- (1) Smith, G. V., and Smith, O. W.: *Am. J. Physiol.* 100: 553, 1932. (2) *Idem*: *Am. J. Physiol.* 98: 578, 1931. (3) *Idem*: *New Eng. J. Med.* 215: 908, 1936. (4) Smith, G. V., Smith, O. W., and Pincus, G.: *Am. J. Physiol.* 121: 98, 1938. (5) Pincus, G., and Zahl, Paul A.: *J. Gen. Physiol.* 20: 879, 1937. (6) Pincus, G.: *Cold Spring Harbor Symposia on Quantitative Biology* 5: 44, 1937. (7) MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A.: *J. Biol. Chem.* 115: 435, 1936. (8) Fieser, L. F.: *Chemistry of Natural Products Related to Phenanthrene*, 1936. (9) Venning, Eleanor H., and Browne, J. S. L.: *Endocrinology* 21: 711, 1937. (10) Browne, J. S. L., Henry, J. S., and Venning, Eleanor H.: *J. Clin. Investigation* 16: 678, 1937. (11) Westerfield, W. W., and Doisy, E. A.: *Ann. Int. Med.* 11: 267, 1937, and personal communication. (12) Allen, W. M.: *Am. J. Physiol.* 100: 650, 1932. (13) Zuckerman, S.: *Proc. Royal Soc. London* 124: 150, 1937. (14) Venning, Eleanor H.: *J. Biol. Chem.* 119: 473, 1937. (15) Weil, Paul G.: *Science* 87: 72, 1938. (16) Smith, O. W., and Smith, G. V.: *AM. J. OBST. & GYNEC.* 33: 365, 1937. (17) Smith, G. V., and Smith, O. W.: *Surg. Gynec. Obst.* 61: 175, 1935. (18) Kellogg, F. S.: *Am. J. Surg.* 35: 300, 1937.

DISCUSSION

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Two new concepts in gynecologic endocrine diagnosis have been presented by Dr. Smith. The first of these is the estriol/estrone ratio, which is, as I understand from his presentation, normally high during the luteal phase of the cycle, low at the time of menstruation, and before labor. It is pathologically low during periods of dysfunctional flowing and in pre-eclampsia. Estriol in general is present during times of corpus luteum activity.

The second point is the demonstration of a hitherto unknown estrogen in human urine, probably to be regarded as estradiol. This "x" estrogen is found to be increased at the time of menstruation, in dysfunctional flowing and in pre-eclampsia. Its presence is evidence of low corpus luteum activity.

These observations are of importance in two directions. First, they promise a new method of investigation. Second, they have already offered new insight into conditions underlying important gynecologic and obstetric diseases.

The hypothesis that the vascular phenomena responsible for endometrial flow may be induced by toxic concentration of non-estrogenic breakdown products resulting from a destruction of the estrogens seems, however, difficult to reconcile with certain experiments producing artificial menstrual bleeding. As you know, women without ovaries have had menstruation experimentally induced by giving an estrogenic substance, and then more or less abruptly discontinuing it. It is difficult to see why this reduction in estrogenic administration should be associated with an increased destruction of estrogens.

The findings in the toxemias of pregnancy interest me particularly, because we have been carrying on somewhat similar investigations recently at the New York University Medical School. In general we agree with Dr. Smith on his previously reported findings of low total estrogens and on his report today of a lowered pregnandiol. We have not attempted the separation of the three different estrogenic substances.

Many reasons combine to make me hesitant in reaching conclusions on this subject.

First, in our experience it has been extremely difficult to fix the normal values for estrogenic substance in the urine of pregnant women, even at a given period of gestation. The figure varies not only from individual to individual, but even in the same patient from week to week.

Second, the diagnosis of the specific toxemia of pregnancy is a very unstable one. Differences in the distribution of cases into such groups as chronic nephritis, specific toxemia and essential hypertension may profoundly affect conclusions drawn from hormone studies.

Probably the greatest difficulty is in the interpretation of the figures obtained. Are the abnormal values in the urine related to the cause, or are they simply the result of the pre-eclampsia? The amount of an estrogen excreted during pregnancy depends on three or four factors, namely:

1. The amount produced in the placenta.
2. The amount destroyed, probably in the liver.
3. The amount converted, perhaps in the uterus.
4. Possibly upon a renal threshold which may exist for the conjugated substance if not for the free estrogens.

In the determination of pregnandiol it will be remembered that the substance actually measured is sodium pregnandiol glucuronidate. If conjugation with glucuronic acid, which is probably dependent on a liver function, fails, the substance will not be detectable in the urine by present methods.

Since lesions of the placenta, kidney, and liver are recognized to occur in pre-eclampsia, is it not possible that the changes in the quantitative relationships of the estrogens in the urine are the result of renal, placental, or hepatic disorders and are not related to the underlying cause of eclampsia?

One question I would like to ask in regard to the theory of treatment, and that is why should one give both estrogen and progesterone in cases of pre-eclampsia? Would not the progesterone alone be as effective in reducing the supposed estrogen destruction?

DR. R. A. ROSS, DURHAM, N. C.—Since the work of Brown and Venning, Hamblen has been working on the metabolism of progestin. We feel that pregnandiol is a test of the utilization of progestin. This is based on the fact of a decrease in its output in a woman who is bleeding or if the endometrium is removed by curettage or if the uterus is removed and the ovaries remain intact. These findings are of special interest in view of what Dr. Smith has said. He has shown by a diagram the possible interplay and alteration of the sterols. Also, Hamblen has been able to recover only 65 per cent in the urine of a known injected quantity. In order to know as much as possible about these products, we must know the amount elaborated, the question of their utilization, alteration, and excretion. In a pregnant individual the fetus and its appendages, the corpus luteum of pregnancy, and the decidua all are complicating factors.

We have not been able consistently to find the alteration in the gonadotropes of the urine and blood in the toxemic patients. He has mentioned changes in the estrogen in the toxemias, and appropriately uses serum estimates as well as urine estimates.

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Smith's excellent presentation throws new light on several old problems, such as, for example, that of functional bleeding. Concerning the hormonal mechanism of the latter, the common assumption has been that the responsible factor is a prolonged and excessive estrogenic influence upon the endometrium, the periodic bleeding phases being due to drops in the level of these estrogenic principles. Dr. Smith's studies, however, indicate that we may have to consider not only this factor of hormone deprivation, but also, and perhaps more importantly, departures from the normal balance of the various chemical forms of estrogen. He emphasizes that the hormonal content of the urine represents merely the balance between hormone utilized and that which is destroyed, and that progesterone plays an important rôle in the regulation of this balance. The bearing of such studies upon our interpretations of urinary hormone assays is obvious.

In his discussion of both functional bleeding and pre-eclamptic toxemia, he referred to the possibility that estrogenic products might be the cause of the vascular changes associated with these conditions. I have long felt that there must be some such liaison between the hormonal factors concerned in functional bleeding and the vascular apparatus of the endometrium, especially the so-called spiral arterioles. After all, normal functional bleeding, like that of normal menstruation, is a primarily vascular phenomenon. The peculiar "blanching and blushing" phenomenon which Markee has described, and which is due to alternating phases of vasoconstriction, vasodilatation in these arterioles, is an essential part of normal menstruation, and it is certainly linked up with the normal factors of menstruation. Departures from the normal hormonal interplay must bring about abnormalities in this vascular response, and here one may expect to find the explanation of the local causes of functional bleeding. Concerning the latter there is still much uncertainty, some holding that the bleeding is due entirely to the occurrence of infarct-like necrobiotic areas, while others feel that in addition there must be an increased permeability of the blood vessel walls. Here lies a fertile field for studies of the sort which Dr. Smith has described today.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS. (closing).—It is quite obvious that all of this material is still in the realm of pure research. Our own enthusiasm for it is because it seems to shed a little light down a dark alley. That is, it gives us a lead toward the possible mechanism that results in menstrual bleeding and in pre-eclampsia, namely, a possible cause for the arteriolar spasm of these states.

Our reason for postulating that breakdown products of estrogen destruction may be concerned in the arteriolar spasm of these states is based on the following: experimental endometrial bleeding has been produced both in monkeys without ovaries and hypophysis and in monkeys without ovaries and adrenals.

Apparently all that is needed for flowing is a live monkey with an endometrium that has been under the influence of estrone. Although necessary for endometrial bleeding, estrone itself is not the actual cause of the bleeding. Our line of thought has been that the bleeding factor, which we are convinced must exist, is due to something that estrone does or something that is done to estrone, or possibly both. And since estrone disappears in the face of increased estrogen production at the time of menstruation and at the onset of pre-eclampsia, we are guessing that its destruction yields the responsible factor.

Dr. Taylor raises the question as to whether the pathology of pre-eclampsia may not be the cause rather than the result of the changed metabolism of estrogens, and suggests the possibility that the conjugating mechanism of estrogen and progestin may be consequently upset. We feel that one would expect in that case much more marked disturbances in the blood and urinary chemistry. Furthermore, our observations indicate an actual deficiency of progestin in this disease, not only on the basis of urinary pregnandiol but also on the basis of urinary estrone, estriol and "x" estrogen.

The reason we have used estrogen in therapeutic trials is because it depresses the high serum anterior pituitary-like substance. Speaking of this substance raises a point regarding discrepancies in the results of assay. Neither Dr. Taylor nor Dr. Ross has confirmed our finding of high anterior pituitary-like substance in toxemia, and I wonder if this is not due to their use of urine for assay instead of serum, since there is so much more chance for error in the collection as well as the assay of urine.

THE PLACE OF VAGINAL HYSTERECTOMY IN PRESENT-DAY GYNECOLOGY*

W. C. DANFORTH, M.D., EVANSTON, ILL.

(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Evanston Hospital)

DURING the past few years a number of papers have been presented to this Society upon the technic and indications of total and subtotal hysterectomy and upon the management of prolapse. As a sequence to these contributions I wish to discuss the indications and technic of vaginal hysterectomy. While I do not believe that all excisions of the uterus should be vaginal, I do believe that in many clinics a greater use might be made of this operation. Until five years ago this operation was done very rarely by us. This was because, in my earlier years, I became prejudiced against the operation. A few years ago my associates and I became convinced that a mode of treatment which was, in some cases, very valuable, was being neglected, and that, in order to give our patients the benefit of the method best fitted to their individual cases, we should make use of either the abdominal or vaginal route. Since that time we have done vaginal hysterectomies 266 times. During the same period 541 abdominal hysterectomies have been performed. This will evidence that we have not displayed the zeal of the convert in employing this procedure in all of our work. We believe, in the light of our experience up to this time that vaginal hysterectomy may be wisely employed in a number of groups of cases.

INDICATIONS

Functional bleeding	48
Prolapse	97
Fibroids	30
Retrodisplacement	33
Moderate descensus—outlet relaxation	55
Carcinoma of corpus	3
	<hr/> 266

Functional Bleeding.—We have done vaginal hysterectomy in 48 cases to control nonmalignant bleeding. Some years ago we gave up irradiation in these cases except in women in the later forties, as our experience showed that the discomforts of a menopause brought on some years sooner than it otherwise would have appeared were greater than those accompanying a surgical procedure. The removal of the uterus vaginally, unless the operation is otherwise contraindicated, affords a very satisfactory method of dealing with this condition. The cervix in many of these cases is in an unhealthy condition. The operation disposes of

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

it and any needed plastic work can be done at the same time. While there appears to be reason for believing that, if menstruation is stopped, the ovaries continue to function but a few years longer, these added years are usually sufficient to carry the woman to the time at which she would normally have had her menopause. The women treated in this way have been far more comfortable than those formerly treated by irradiation.

Fibroid Tumors.—In women in whom parturition has caused the uterus to be fairly movable, so that the cervix may be pulled down into the lower third of the vagina. We would exclude tumors too large to be easily delivered through the vaginal incision. We have in a few cases removed by morcellation tumors too large to be easily delivered, but we prefer in most cases to remove the larger tumors by abdominal section. Certainly morcellation is not an operation for the surgeon unskilled in this field. Intraligamentous tumors do not lend themselves to vaginal removal, and fibroids which have invaded the subvesical space are not good cases for vaginal operation. Fibroids associated with previous inflammatory disease which has left residues which diminish the mobility of the uterus and which may have left extensive adhesions, are best excluded from vaginal operation. We have done 30 operations for the removal of uteri containing fibroids.

Retrodisplacement.—In women in whom further childbearing is undesired or unwise, whose uteri are heavy and large, and in whom the uterus is fairly movable, this operation may serve a useful purpose. It is best reserved for the women who are in or near the menopausal years. It should not be done in the younger women. Often in these cases outlet relaxation demands attention and an unhealthy cervix is present. I believe that at least part of the relief which follows vaginal hysterectomy done for this condition is due to the fact that it disposes of the varicose veins of the broad ligament which so often accompany it. We have done 33 operations for this indication.

Prolapse and Descensus.—In cases in which the uterus protrudes partially or wholly from the introitus, we, in almost all cases, make use of vaginal hysterectomy. An occasional Manchester operation is done. Rarely, in a feeble old woman a LeFort operation is employed, and, occasionally, in women past childbearing or who are to be sterilized, and when the descensus does not cause the cervix to pass the introitus, we employ transposition of the uterus, with or without amputation of the cervix. Occasionally, in minor degrees of descensus, the bases of the broad ligaments are detached and fastened in front of the upper part of the cervix, often with amputation of part of the cervix. In all other cases vaginal hysterectomy is the procedure of choice. For extensive descensus or prolapse no form of abdominal suspension is used. We have done 97 vaginal hysterectomies for this indication.

Contraindications.—Our experience has impressed upon us that certain conditions make it unwise to adopt this method of approach. One of the most important of these is changes in intra-abdominal conditions produced by a previous operation. Adhesions of omentum or intestine

may cause the operation to be far more difficult and hazardous than it would otherwise be. Certain procedures, as retrodisplacement operations and ventral fixations, when the uterus has subsequently come down, cause vaginal excision to be particularly difficult. We have done a few such cases. The great majority of these should be attacked from above. Ventral fixation should be an obsolete procedure but upon two of the women upon whom we performed vaginal hysterectomy this operation had previously been done. In these two cases, although the uterus had later come down, the elongated band which connected the fundus uteri to the abdominal wall rendered it impossible to deliver the uterus either anteriorly or posteriorly. Pressure over the lower abdomen by the hand of an assistant aided materially in reaching the band at the fundus which it was necessary to divide. It is usually wiser to deal with these cases otherwise than vaginally. When doubt is felt as to the practicability of the vaginal operation because of adhesions, a posterior colpotomy may be done. If the uterus is of normal, or nearly normal, size, its surface may be palpated and information obtained as to the presence or absence of adhesions. The operation may continue vaginally or the colpotomy would be closed and the uterus removed abdominally after completing any needed plastic work. In general, if doubt is felt, it is best to operate abdominally.

It is better not to attempt to remove the uterus vaginally if there has been a preceding pelvic inflammation sufficiently severe to cause adhesions of bowel or omentum in the pelvis. A deft and experienced operator may deal with these cases but it is usually better to attack them from above.

We have, in a few cases, removed by morcellation, fibroid tumors which were too large to be delivered vaginally. This is a procedure which may be carried out by one who has developed a considerable skill with this operation but should not be attempted by others. It is very useful, if one has misjudged the size of a tumor, for it may be removed by morcellation with far less trauma to the patient than would be caused by forcefully delivering a large mass through an opening of insufficient size. We use it only occasionally.

In many cases of carcinoma of the corpus uteri the size and mobility of the uterus would render vaginal removal possible. In addition, many women with cancer of the uterine body have more or less outlet relaxation which would facilitate the operation still more. We do not believe, however, that vaginal removal is wise and have done it in only 3 cases. In performing abdominal hysterectomy for corporeal cancer, our first move is to place straight clamps close to the uterus on either side to prevent carcinoma cells from being pushed into the parametrium through the lymphatics and blood vessels by unavoidable manipulation of the uterus. The upper part of the broad ligaments cannot be blocked off if the operation is being done vaginally until a late stage of the operation. If there were also a marked descensus, this disadvantage might be less. The tenaculum in delivering the uterus is a disadvantage as it should be traumatized as little as possible. In these cases the ab-

dominal operation is usually preferable. We have not considered vaginal hysterectomy as a means of managing carcinoma of the cervix as our usual means of treatment is irradiation.

Ovarian Tumors.—If hysterectomy is to be done upon a patient who also has an ovarian cyst, it is usually wiser to operate abdominally. We

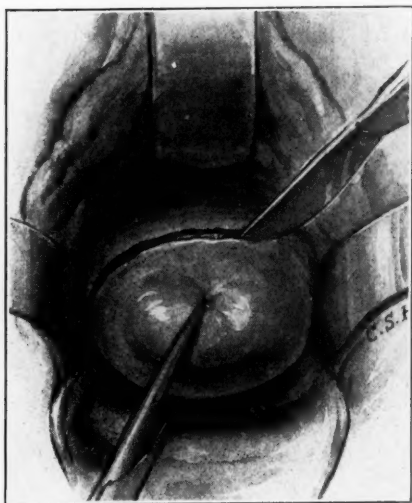


Fig. 1.

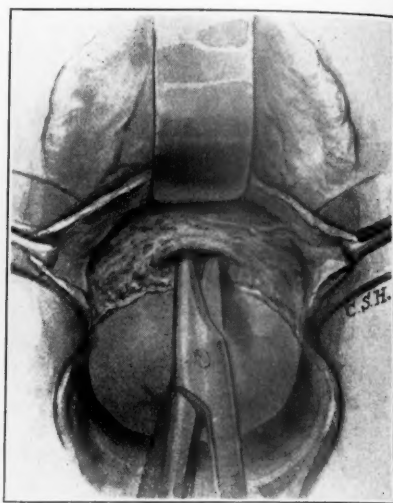


Fig. 2.

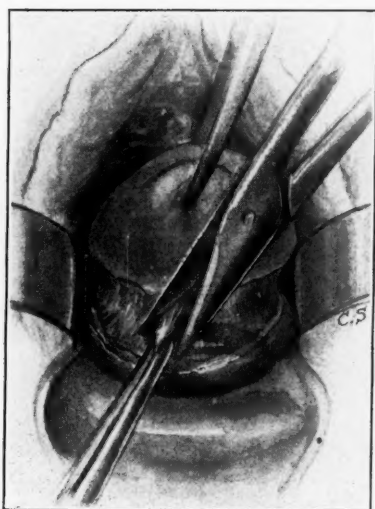


Fig. 3.

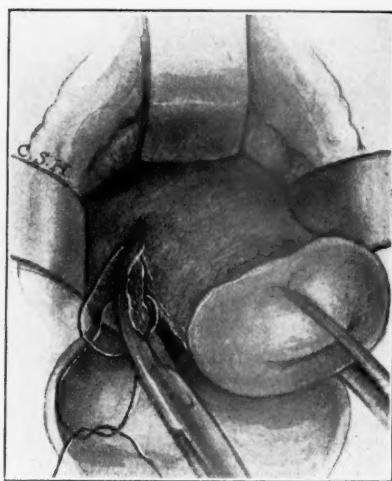


Fig. 4.

have, however, removed a number of cysts while doing vaginal hysterectomy. Cysts of moderate size and which are not adherent may often be removed easily. In one case unexpected adhesions were encountered, which rendered the operation more difficult, but did not prevent its completion without incident. Our present position is, that if hysterectomy

tomy is to be done and an ovarian cyst is present, unless the cyst is freely movable and of such a size that it may be removed with reasonable ease, and unless the operator feels at home in the vaginal field, abdominal section is preferable. Should either a dermoid or a malignant cyst be suspected vaginal approach should not be considered. Unless the cyst is small it must be punctured before removal, which is unsafe in either of these. In some European clinics vaginal removal is practiced even though the cyst be large. We prefer a more conservative attitude.

In stating a number of quite definite contraindications, we indicate clearly that we do not feel that this procedure should be used in all cases. We believe that the gynecologic surgeon should be master of both

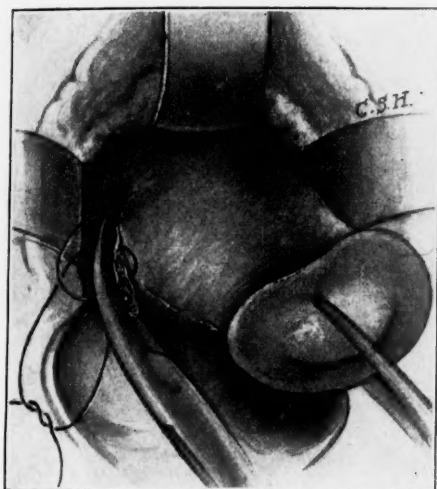


Fig. 5.



Fig. 6.

methods, and that his choice of the procedure to be used in a given case should be based wholly upon the conditions found in that case and not influenced by a preference for one or a feeling of inability to use the other.

TECHNIC

After trying various ways of doing the operation we have settled fairly well upon two procedures. For the marked descensus with the uterus protruding partly or wholly from the vagina the procedure sometimes called the Mayo operation, but which was probably first done by J. Riddle Goffe, has been very satisfactory. The technique of this operation has been well described and illustrated by George Gray Ward. It is of the greatest importance that the uterosacral ligaments be united by transverse sutures and in some cases in which the descensus is extreme, that the pouch of Douglas should be dissected out. This removes the hernial sac through which the accompanying enterocele descended and closes the hernial opening. Failure to attend to this essential point of technic may cause a later protrusion at the posterior vault. Failure to appreciate this fact caused one recurrent enterocele,

the anterior portion of the repair in this case remaining intact. In one other case a complete failure occurred necessitating later operation.

The uterosacral ligaments, after being transversely united, must be attached to the posterior margin of the united broad ligaments in order completely to close the posterior portion. The anterior edges of the united broad ligaments are attached on either side of the urethra underneath the rami of the pubes in order to retain the bladder. Incontinence of urine may be dealt with as the operation proceeds, and, if fascial flaps are available in the anterior wall, they are dissected free and united. A perineal plastic completes the operation. A small rubber or gutta-percha drain is usually used at the mid-point of the suture line in the vault.

For the cases in which a marked descensus is not present, it is not necessary to open the anterior vaginal wall unless incontinence, cystocele, or urethrocele is present for which plastic work is needed. A simple incision at the lower limit of the bladder is made. The bladder is freed from the anterior uterine wall by scissors dis-

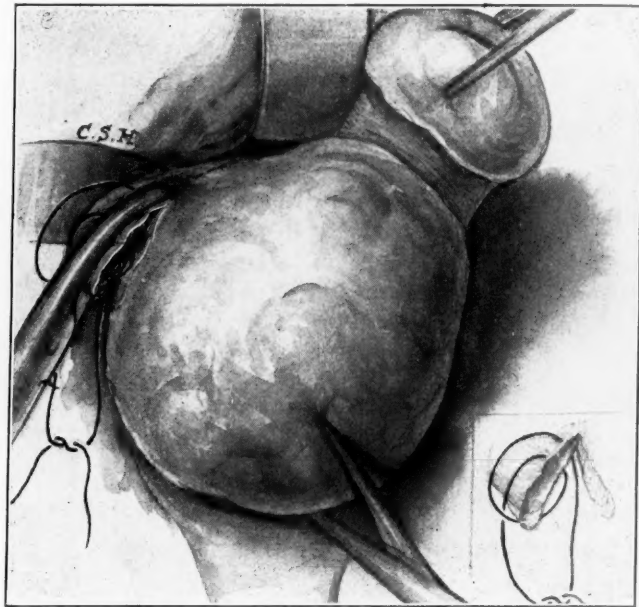


Fig. 7.

section and pushed upward. The anterior peritoneum is opened, or, if it is not easily identified, it is left until later. The incision is extended around posteriorly and the posterior peritoneal pouch opened. The uterosacral ligaments are caught on either side with clamps, cut and the clamps replaced by suture ligatures. It is better to replace all clamps at once by suture ligatures for two reasons. First, a clamp allowed to remain may slip and cause bleeding, and, second, the removal of clamps at once gives more space and greatly facilitates later work. As the uterosacral ligaments and the bases of the broad ligaments are divided the uterus may be brought lower, and, if the anterior peritoneum has not been opened, it may now be done easily. When sufficient of the uterine supports have been divided the corpus is delivered. We have found the delivery of the uterus through the posterior vault, instead of anteriorly as is usually suggested, a very satisfactory measure. This was suggested to me by Heaney, but I have since learned that it was done forty years ago by Joseph Price. It is easier and usually requires less force than delivery anteriorly. Two clamps are placed on either side, and the uterus is removed.

In closing the wound, it is best to attach the stumps of the broad and round ligaments and the uterosacral ligaments to the vaginal angles. This is done by passing a suture through the anterior vaginal wall and peritoneum, through the stumps of the broad, round, and uterosacral ligaments, and lastly through the posterior peritoneum and vaginal wall. This supplies support for the vaginal wall and also brings together the peritoneum of the anterior and posterior leaves of the broad ligaments and of the pelvis, thus leaving a good peritoneal covering. Closure is completed by interrupted sutures between these two. Occasionally a suture outside one or both of the two first sutures is needed to bring the vaginal wall together completely. Drainage is needed only exceptionally. The most annoying bleeding is usually from the cut edge of the posterior vaginal wall. A temporary suture is sometimes used to control this. This mode of closure approximates the vaginal walls so that the anterior and posterior walls lie smoothly in contact. Approximation of the wound in the vault by an anteroposterior suture line disturbs the normal relationship of the anterior and posterior walls and also may, as the lateral vaginal structures are drawn inward, tend to displace or kink the ureter. A transverse suture line is preferable.

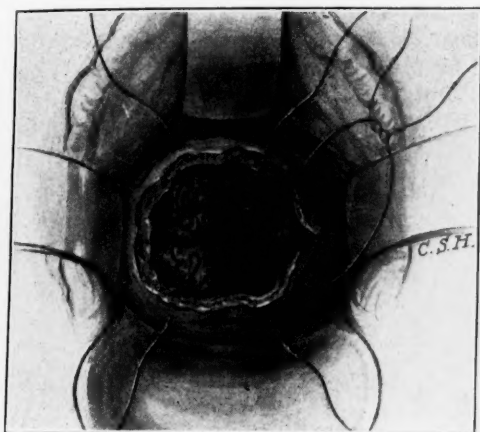


Fig. 8.

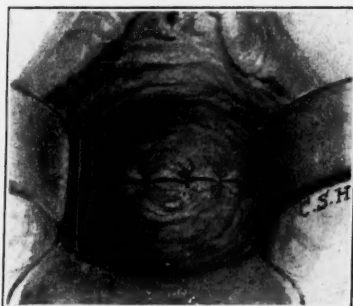


Fig. 9.

RESULTS

In this series of 266 cases there were no deaths. This statement does not mean that the operation is without mortality and we freely admit, while every care has been used, that good fortune has also played a part and we do not expect to operate indefinitely without mortality. During the time covered by this report, 451 subtotal hysterectomies were done. In this same period 90 total hysterectomies were done. The freedom from symptoms referable to the cervix in our vaginal cases has caused a greater use of the total operation during the latter part of this time. Of the total number of hysterectomies 31.5 per cent were done vaginally.

The postoperative course of these cases has been smoother, on the average, than a similar number of abdominal hysterectomies. The advantage of vaginal attack is most apparent in older women, particularly those operated upon for marked descensus. While the morbidity was a little greater in this group than in those operated upon by the simple technic used in operations done for other indications, recovery

has been far smoother than would be expected in a group of similar age upon whom a combined vaginal and abdominal operation had been done. The fact that in the cases of marked descensus or prolapse the operation is almost extraperitoneal doubtless contributes a great deal to the smoothness of the recovery.

COMPLICATIONS AND MORTALITY

Cystitis and pyelitis	6	2.26%
Postoperative bleeding	4	1.5 %
Phlebitis	2	0.75%
Pelvic abscess	1	
Total morbidity	9.02%	
(American College of Surgeons Standard)		
Mortality	0	

In this group we had a morbidity rate of 9.02 per cent, using the American College of Surgeons standard, that is, a rise to 100.4 per cent on any two days excluding the day of operation. An attempt to extend the applicability of the vaginal route greatly beyond the limitations already stated would almost certainly be followed by an increased mortality and morbidity. This would certainly be so in the hands of operators not thoroughly at home in the vaginal field.

An objection which is sometimes made is that the vaginal operation shortens the vagina. This we find to be true in many of the patients operated upon for prolapse. The shortening is not extreme and in many of these older patients is of little importance. In the women operated upon for indications other than prolapse, in whom the technic shown in the illustrations is used, there is no shortening.

OPERATIVE COMPLICATIONS

In two cases an injury of the bladder occurred. Both were recognized at once, the wound closed, and recovery was uninterrupted. In one case active bleeding from the uterine artery occurred due to the slipping of a clamp. This was controlled before serious loss of blood. There were 4 cases of postoperative bleeding. In one of these the bleeding had nothing to do with the hysterectomy but came from the perineum, upon which a plastic operation had been done. In the 3 others it came from the region of the uterosacral ligaments and was controlled by placing a six inch clamp, which was left for thirty-six hours upon the bleeding area. Closer attention to this area in closing the operative wound has prevented further bleeding.

In one case a serious thrombophlebitis followed operation. Recovery followed conservative management. In one case a pelvic abscess developed six weeks after operation. This was opened and recovery followed. In two patients who were operated upon for prolapse unsatisfactory results followed. In one case the anterior portion of the reconstruction was satisfactory but an enterocele followed. This was an early case in which the patient was operated upon before we had come to appreciate the importance of careful closure of the posterior peritoneal pouch and the approximation of the uterosacral ligaments.

Our present opinion is, that vaginal hysterectomy is a procedure of great value and that it is worthy of more extended use than it receives in many clinics today. Strongly to advocate its adoption by occasional operators, or by the general surgeon without gynecologic training would probably not be to the advantage of the patients of these men. While a clever general surgeon may learn the technic of this as of other operations, in the hands of most of the individuals who make up these groups, morbidity and mortality would be too high. It is a procedure for the gynecologically trained surgeon. It is more difficult, in some cases much more difficult, than the average abdominal hysterectomy.

In cases to which the operation is well adapted, convalescence is, on the average, smoother than in abdominal cases. Mortality should, in expert hands, be essentially the same in uncomplicated total abdominal hysterectomy and vaginal hysterectomy. A painstaking vaginal toilet is an essential part of either operation.

Although I ascribe a high value to the operation I think that its application should be kept within logical limits. If used in cases such as those discussed under the head of contraindications, the dangers of the operation increase. A careful evaluation of the anatomic and pathologic characters of each case is essential, and the choice of the route of operation must be based upon a consideration of these.

DISCUSSION

DR. JOSEPH L. BAER, CHICAGO, ILL.—When we decide that we are going to try out an operation, we try within reasonable limits to make the patients fit that operation until we have had one, two, or three years of experience with that operation. That is entirely justifiable in the hands of men who are careful of the ultimate welfare of their patients. We did this in our prolapse series when we worked first with the interposition operation, then vaginal hysterectomy, and now parametrial fixation.

Nevertheless we sometimes give way to departmental reactions. For instance, vaginal hysterectomy gives way to total hysterectomy when the supports of the uterus are good, or when the cervix does not come down reasonably well. The vaginal approach is indicated when the cervix is bad and the uterus is mobile, and especially when a plastic operation anteriorly or posteriorly, or both, is necessary. I like parametrial fixation particularly in those instances of greater degrees of prolapse than those which Dr. Danforth prefers. Partial protrusion of the uterus is usually protrusion of the cervix, and I see no reason for not utilizing parametrial fixation for that type of prolapse instead of vaginal hysterectomy. We likewise use the Le Fort operation more than do Dr. Danforth and his group. I like it for the elderly woman with the atrophic uterus.

The essentials of technic in vaginal hysterectomy are these: First, during the closure of the opening which we have created at the top of the vagina, we must anchor the vaginal vault one way or another. Second, when the bladder has prolapsed, bladder and urethra must be elevated and the supports properly reconstructed. Third, when there is a deep cul-de-sac, that must be completely repaired. We do not drain either in the ordinary types or in the prolapsed types of vaginal hysterectomy. There should be no necessity for drainage in the vaginal vault nor packing of the vagina.

In the actual technic my associate, Dr. Reis, is trying to convert me to the amputation of an unduly long cervix after it has been completely separated and before rotating the uterus on its transverse axis. In that way the uterus is almost ball-like and can be rotated equally freely anteriorly or posteriorly.

When the cul-de-sac is opened I think it worth while tipping the table and putting the patient in a partial Trendelenburg position. Occasionally the patient strains and exerts a little intra-abdominal pressure so that loops of bowel may present at the vaginal vault. It is simpler to tip the table at that stage of the operation than to pack bowel away.

I like the transverse closure of the vault. Ordinarily I do not unite the uterosacrals in the midline. I do, however, when they are unusually long, or when there is enterocele.

Our morbidity is more than double that shown by Dr. Danforth. We had one fatality in a private patient of my own which I think it proper to report at this time. After an ordinary uneventful hysterectomy she developed fever and on the fourth day we instituted sulfanilamide therapy in rather considerable doses. The patient developed an intense rash with urticaria, which went on from pink to purple in color, and in the week following, in spite of every measure that we could institute, the termination was fatal.

DR. LILIAN K. P. FARRAR, NEW YORK, N. Y.—Dr. Danforth has called attention to other conditions than prolapse that might be operated upon by the vaginal route. I am glad to learn that he prefers to do a vaginal hysterectomy rather than apply radium in functional bleeding in women at the time of menopause. By vaginal hysterectomy the cervix does not remain a menace for the rest of a woman's life, as after irradiation of the fundus, and a more comfortable menopause is secured for the patient if the ovaries are left at operation and not destroyed by irradiation. By restricting the vaginal operation to uteri and to ovarian neoplasms that are not so large but that one can be sure of their easy delivery through the pelvis, to retroversion or to chronic adnexa if not adherent, one may do vaginal hysterectomy and all needed plastic work in less time than a combined vaginal and abdominal operation, and with less shock. I believe though that a known or even suspected carcinoma of the fundus should be done by the abdominal route with clamps applied to the sides of the uterus as Dr. Danforth does.

There are several points in technic that I would like to speak of and the first is the closure of the wound anteriorly. Dr. Danforth says, "The anterior edges of the united broad ligaments are attached on either side of the urethra underneath the rami of the pubes in order to retain the bladder." This is never necessary in total abdominal hysterectomy, why is it necessary in vaginal hysterectomy? It causes distortion of the upper pelvic floor, displacement of the ureters and may produce an enterocele.

The bladder was in its normal position resting upon the uteropubic fascial plane, with a split in the fascia which was the beginning of a cystocele. Dr. Danforth says, "If fascial flaps are available in the anterior wall they are dissected free and united." I have never seen a case where these flaps could not be dissected free and when sutured together the constructed fascial plane may then be sutured by its posterior edges transversely to the broad ligaments exactly as we do in total abdominal hysterectomy and restore the bladder to its normal position in the pelvis.

The final point is the repair of an enterocele. This condition has long been of interest to me since I saw the monumental work of Tandler and Halban ("The Anatomie und Aetiologie der Genital Prolapse"). I believe that to repair an enterocele correctly one must dissect it out and suture the uterosacral ligaments together.

PROFESSOR LUDWIG ADLER.—Dr. Danforth's mortality record has been excellent and I must confess that we have not been as fortunate as he has been. This may in part be due to the fact that our indications are somewhat different from Dr. Danforth's. A great number of his cases were of prolapse or of descensus. We have used for such cases either the interposition operation or a procedure similar to that of Fothergill, or in old women the Le Fort operation. Following hysterectomy for prolapse we have seen quite a number of recurrences in the form of hernia of the vagina, and therefore, prolapse in our country is rarely considered an in-

dication to perform a vaginal hysterectomy. On the other hand, we do vaginal hysterectomy as a method of choice in fibroids if the tumor is movable even if the uterus is double the size of a fist.

For the treatment of bleeding in a uterus which has no fibroids, I personally have been using intrauterine radium treatment, but with so small a dosage that the troubles of menopause do not occur. It seems to me that this treatment is less dangerous than the complications which sometimes follow vaginal hysterectomy.

As to the technic I usually bring out the uterus from the anterior plica. In some cases the procedure of bringing it out from the pouch of Douglas is advisable. If the uterus is not easily movable or if the uterus is large, amputation of the cervix is useful. If there is difficulty in bringing out the uterus, as in inflammatory cases, or when large fibroids are present, we split the whole uterus or perform a morcellation. One point which seems very important to me is that all the stumps should be placed extraperitoneally. Furthermore, if we remove the adnexa, we take care that the corner suture of the peritoneum catches the infundibulopelvic ligaments. We do this for two reasons: first, to prevent adhesions, and second, because if there is hemorrhage from one of the vessels it can be controlled without opening the peritoneum. After closing the peritoneum I always tie the stumps to the corner of the vagina so that there is a retraction of the vagina which prevents later descent.

We do perform the vaginal operation as a routine operation for cancer of the body if the uterus is not too large.

May I add that personally within the last twenty years I have done nearly all of my vaginal operations, including uterine cancer, under twilight sleep and local anesthesia. It has not only the effect of lessening the shock of operation, but the bleeding is less and the dissection of tissues becomes very easy.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—Since using ethylene gas for anesthesia I have done 831 vaginal hysterectomies in nonmalignant disease with 3 fatalities as previously reported. Most of the operations were done for fibroids. Among these cases were 197 nulliparous patients. Some of these were with intact hymens so that the hymen had to be incised in order to enter the vagina. In the last 369 vaginal hysterectomies, it was necessary to morcellate 93 times. In this list I have not included cases of carcinoma of the body of the uterus which I prefer to operate upon rather than to irradiate. Whenever possible I operate upon these cases vaginally, because they are for the most part elderly women and will stand a vaginal operation much better than an abdominal one. There has been no mortality in these cases of cancer of the body of the uterus.

For a considerable length of time now I have been operating upon the cases of carcinoma of the cervix after they have been treated with radium and have healed, hoping in this way to increase the number of ultimate cures. I do either a Schauta or a Wertheim on these cases, depending upon the conditions.

DR. DANFORTH (closing).—Recently we have been doing two-thirds of our hysterectomies by the abdominal route and only one-third from below. The choice of procedure is an individual matter. One who has developed a great deal of skill can take out almost any uterus vaginally if he chooses to do it. Whether it is wise to do so from the standpoint of the patient's safety is another thing and I think one should choose the operation which is safer for the patient and that causes certain limitations.

Transverse closure has a definite advantage in that it does not drag in the walls of the vagina and is rather less likely to produce kinking of the ureter.

Dr. Adler's point about bringing the stumps of the ligaments into the vaginal angle is very important. We find it useful except when we are dealing with prolapse.

As our skill increases with an operation we are inclined to use it more and more. We find ourselves sometimes getting a little more liberal in the use of the operation, but I think this should not be done until one increases one's skill.

HYPERTENSION AND PREGNANCY*

WILLIAM J. DIECKMANN, S.B., M.D., AND IRA BROWN, A.B., M.D.,
CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, The University of Chicago,
and The Chicago Lying-in Hospital)*

WE HAVE analyzed the records of over 1,200 toxemic patients, treated by us during a six-year period, to determine the importance of hypertension in pregnancy and the practical value of a new classification of the toxemias. It has been our belief for some time that hypertensive arterial disease is the primary condition in many of the so-called "toxemias of pregnancy," and that the edema and albuminuria which may occur in this type of toxemia are secondary to the vascular condition. Other investigators have assigned as much importance to the presence of edema or proteinuria as to the hypertension. Such an assumption presupposes some type of kidney lesion to explain the albuminuria and either a renal lesion or an abnormal tissue physiology to account for the edema. This difference in the interpretation of the significance of these signs is largely responsible for the somewhat chaotic condition of the classification of the toxemias of pregnancy.

Prior to 1926, patients with toxemia of pregnancy were divided into eclampsia, pre-eclampsia, and nephritic toxemia or chronic nephritis. The latter condition was likely to recur in subsequent pregnancies, and usually between pregnancies there was a hypertension and often an accompanying proteinuria.

Stieglitz in 1926 stressed the importance of hypertension in pregnancy and divided the toxemic conditions into: (1) those due to the pregnancy, eclampsia, and pre-eclampsia; (2) those due to a pre-existing vascular and/or renal disease; and (3) those due to thyrotoxicosis and acute nephritis.

The same year Stander and Peckham published their report which grouped patients with toxemia into eclampsia, pre-eclampsia, chronic nephritis, and low reserve kidney. The latter condition was distinguished by a moderate hypertension, a small amount of albumin in the urine and slight edema. These abnormal findings had disappeared by the end of the puerperium, and, although the condition returned with each pregnancy, there was no increase in the severity of the signs and no demonstrable damage to kidney, heart, or vascular system. Since their original paper, Stander and Peckham in separate reports have admitted that the diagnosis of low reserve kidney has often been incorrect. Finally, Stander in 1938 stated that the low reserve kidney might be a mild form of pre-eclampsia. He also stated that the term "chronic nephritis" as used by him implied kidney damage due either to a previous acute glomerulonephritis or to a nephrosclerosis.

Herrick and Corwin in their first report, in 1927, stressed the importance of hypertensive arterial disease complicated by pregnancy. Eclampsia and chronic nephritis were additional groups.

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

Patients with toxemia of pregnancy at the Boston Lying-in Hospital since 1936 have been divided into the following groups:

A. There is evidence of disease independent of pregnancy: (a) Nephropathies associated with arterial vascular disease, (b) inflammatory nephropathies, (c) degenerative nephropathies.

B. There is no evidence of disease independent of pregnancy: (a) Pre-eclampsia Grade 1, (b) pre-eclampsia Grade 2, (c) eclampsia. Our only objection to this classification is the use of the word nephropathy which implies that there is renal pathology or impairment. No one, so far as we know, has been able to demonstrate any impairment of kidney function or alteration in the urinary sediment in patients with an early essential hypertension.

Formerly we grouped our patients into eclampsia, pre-eclampsia, chronic nephritis, acute glomerulonephritis, and nephrosis, but since 1933 we have restricted the term chronic nephritis to those patients who have had a previous acute glomerulonephritis. Those patients whom we formerly classified as having chronic nephritis are now placed either in a vascular-renal disease or essential hypertension group.

Pregnancy does occur in patients with essential hypertension and vascular-renal disease and since these terms are commonly used by the internist it would seem logical for us to apply them where indicated instead of using vague or possibly misleading terms, such as nephritic toxemia, recurrent or latent nephritis, low reserve kidney, etc. The opinion which some internists have of the obstetrician's knowledge of vascular-renal disease is indicated by the following quotation: "Again the fact must be faced that ignorance of these diseases [toxemias of pregnancy] is abysmal," which appeared in a recent article on hypertension by Page. Furthermore, if such a classification with the addition of the terms pre-eclampsia and eclampsia would meet all requirements for distinguishing the various toxemias of pregnancy, further studies of these conditions would be simplified and there would be less conflict of opinion with the internist. This classification is not original with us but has been used by other investigators in various forms.

Our patients are grouped as follows:

A. Pre-eclampsia.—The appearance in a normal pregnant woman and/or disappearance by six weeks post partum of one or more (or all) of the following: (1) A systolic blood pressure of 140 or more for two days or longer. (2) An edema of at least the ankles and legs which has no obvious etiology. (3) A proteinuria which is present for two days or more (a clean specimen and no urinary tract infection). (4) Cerebral, visual, gastrointestinal, and renal symptoms may also occur.

B. Essential Hypertension.—A systolic blood pressure of 140 or more for two days or longer which is either present before pregnancy or appears during pregnancy, and persists longer than six weeks post partum. As term is approached there may be slight edema and proteinuria. The height of the blood pressure is usually out of proportion to the degree of edema and albuminuria. The renal function is within high normal limits. The ophthalmoscopic examination reveals either a normal retina or at the most only a slight narrowing of the retinal vessels. Occasionally the blood pressure is within normal limits between pregnancies, but it is always very labile, in that the response to various stimuli is abnormal.

C. Vascular-Renal Disease.—This disease is characterized by the presence of any two or more of the following signs: Hypertension, edema, or proteinuria before or

development during pregnancy and their persistence longer than six weeks post partum. The renal function is in the lower limits of normal or it may be below normal. Ophthalmoscopic examination usually shows more marked retinal vessel changes than in the essential hypertension group. Subsequent pregnancies almost invariably intensify the various symptoms and signs. The condition may be the result of a long-standing essential hypertension, pyelonephritis, or chronic glomerulonephritis. The only difference between Groups B and C is one of duration and the amount of vascular and renal pathology. It seems to us that the subdivision of the patients with hypertension into Groups B and C permits a more logical separation of pregnant patients with increased blood pressure, because it will be noticed subsequently that the patients classified as having essential hypertension have many characteristics which distinguish them from the vascular-renal disease group and also from those having pre-eclampsia.

We have divided each group into mild and severe according to the following criteria: A severe case is one in which (a) two or more of the following signs are present: the systolic blood pressure is over 170, proteinuria is over 0.3 per cent or 3+, or there is marked edema of the legs; (b) at least one of the following signs is present: systolic blood pressure is over 200, proteinuria is over 0.5 per cent or the urine solidifies on testing, or there is a generalized edema; (c) the occurrence of one of the signs listed in (a) and the development of marked cerebral, visual, gastrointestinal, or renal symptoms. All other toxemic patients are classified as mild. It is obvious that the amount of protein in the urine and the degree of edema are dependent on personal observation. For the past two years we have been determining the twenty-four-hour excretion of albumin which is a better guide than the daily testing of one specimen. Our only quantitative method for measuring edema is to determine the weight gain during pregnancy. However, with these relatively crude qualitative measurements, we are able to demonstrate marked differences between the mild and severe conditions and between pre-eclampsia, vascular-renal disease, and essential hypertension.

Undoubtedly, mistakes have occurred in classifying and in evaluating the severity of signs and symptoms, but we have not deleted any cases because the diagnosis or degree of severity was questionable. The majority of the patients were seen by us and a tentative diagnosis as to the kind of toxemia and degree of severity was made on discharge from the hospital. However, this report is based on records which were only considered complete at six months or longer after delivery. These charts were classified during the winter of 1937 and again in 1938. Comparatively few diagnoses were changed, but the degree of severity was frequently altered from severe to mild. It seems that as time passes one forgets how sick the patient actually was with the result that the clinical condition has undoubtedly been underestimated in many instances.

Fig. 1 illustrates the effect of age, parity, and surface area. The latter was used because it is a function of the height and weight of the patient. Seventy-four per cent of the pre-eclamptic patients are under 30 years of age, as compared with the vascular-renal group in which only 34 per cent are under 30. Sixty-six per cent of the pre-eclamptic patients are in their first pregnancy, while only 11 per cent of the vascular-renal

group are primiparas. Thirty-five per cent of the pre-eclamptic group, in contrast with 52 per cent of the vascular-renal group, have a surface area greater than 1.7 sq. m. It is obvious that the multipara of 30 years or more and overweight, who develops evidence of toxemia in pregnancy, is more likely to have vascular-renal disease than pre-eclampsia. We

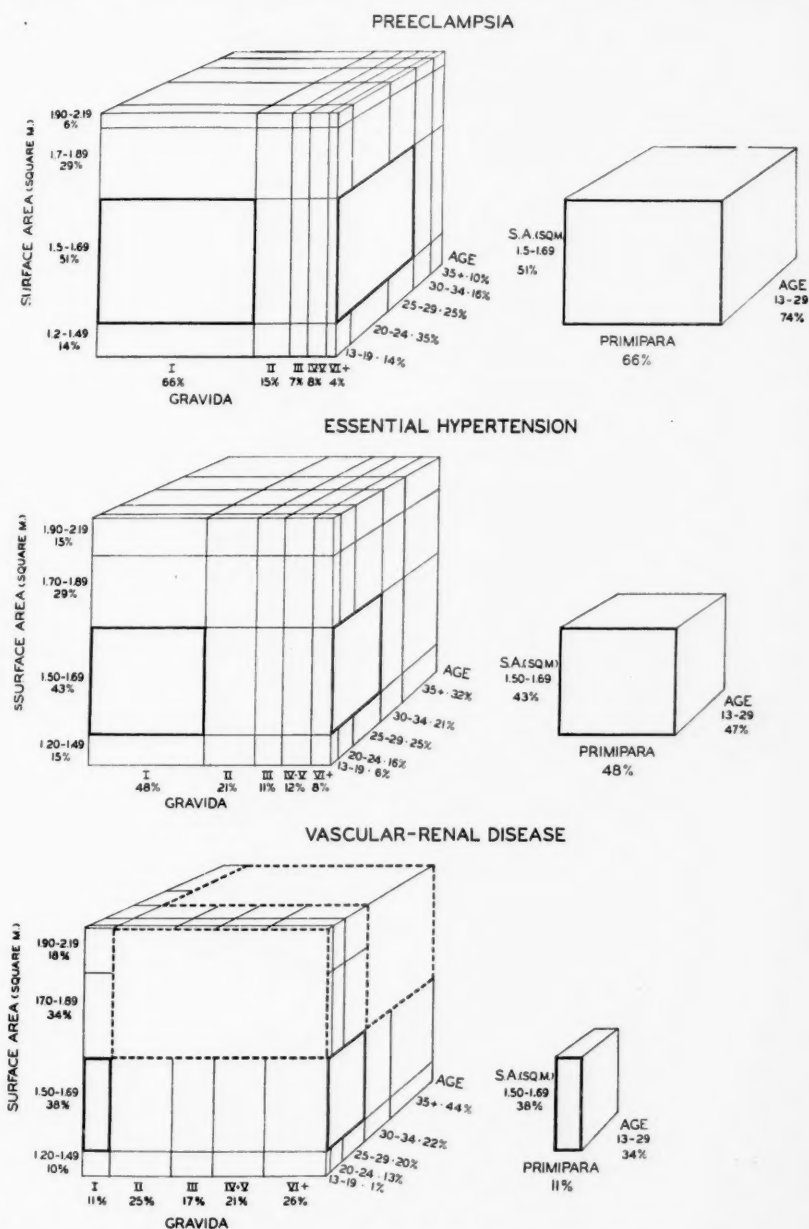


Fig. 1.—Characteristics of modal group as to age, parity, and surface area for pre-eclampsia and comparison with essential hypertension and vascular-renal groups.

do not believe that repeated pregnancies cause the disease, but that they do aggravate and accelerate the disease process. Furthermore, repeated pregnancies usually signify increasing age and many of these women, even if they had had no children, would unquestionably have ultimately developed vascular-renal disease. The hypertension group is intermediate, but the number of older women, of multiparas, and of overweight women is apparent.

The amount of protein in the urine with but few exceptions was determined qualitatively, and as a result there is no correlation with any of the other measurements or signs. Harden, Barker, and other investigators have emphasized the importance of a nitrogen balance in patients with albuminuria, or as Harden termed it, "protein stabilization." However, except in a few patients who had a nephrosis we have not been concerned about the protein loss, because it usually amounts to less than 3 gm. and rarely exceeds 5 gm. per twenty-four hours. We urge that instead of testing a daily specimen, the twenty-four-hour excretion of protein be determined for its diagnostic and prognostic value. Thus we hospitalize the patient when the proteinuria amounts to 5 gm. or more per twenty-four hours, and if this amount persists for several weeks, we know that a high percentage of the fetuses will die in utero because of massive placental infarction, retroplacental hematoma, or abruptio placentae. Excretion of these large amounts of protein usually occurs in the vascular-renal group. The pre-eclamptic patient may excrete as much as 4 per cent protein in the urine, but this concentration is reached only when the urine is very concentrated and the total amount of albumin lost amounts to 1 or 2 gm. The patient with essential hypertension rarely excretes much albumin. The ambulatory patient can save all urine for a twenty-four-hour period, measure it, and bring a sample of the mixed twenty-four-hour volume for protein and chloride analyses. The latter determination will aid in determining whether or not the patient is adhering to a salt-poor or salt-free diet.

The average gain in weight during normal pregnancy, based on published reports and our own data, is 9.4 kilograms. Forty-three per cent of the pre-eclamptic group, 25 per cent of the vascular-renal, and 21 per cent of the hypertension group gained over 10 kilos. Twenty-nine per cent of the pre-eclamptic, 14 per cent of the vascular-renal, and 13 per cent of the hypertension group gained over 12 kilos. The average gain per week of normal pregnant women while under observation amounts to 0.45 ± 0.17 kilos. Seventy-four per cent of the severe pre-eclamptic, 49 per cent of the severe vascular-renal, and 23 per cent of the severe hypertension group gained at a rate greater than 0.6 kilos per week. Thus not only is it important to weigh the patient, but the average gain per week should always be calculated, because quite often it is the first sign of impending toxemia.

The relations between the weight gain per week, systolic blood pressure and presence or absence of edema in the severe groups are depicted in

Fig. 2. The average of the maximum blood pressures over a twenty-four-hour period was calculated and this figure forms the basis for our tables. Edema was described as follows: + means a definite pitting on pressure of the tissues over the lower third of the tibia; ++ means marked pitting over the entire tibia; +++ means that there is an associated edema of hands and face; ++++ means anasarca. Grades ++ and +++ are com-

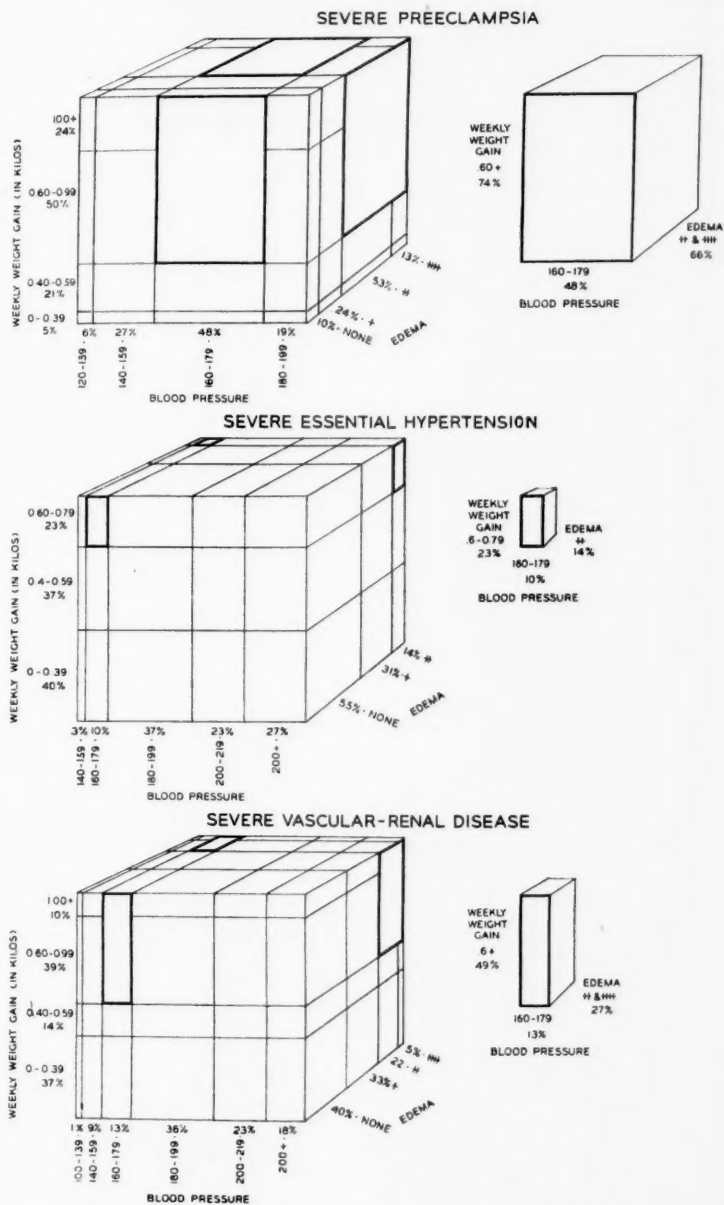


Fig. 2.—Characteristics of modal group as to weekly gain in weight, systolic blood pressure, and presence or absence of edema for severe pre-eclampsia and comparison with essential hypertension and vascular-renal groups.

bined in the figure as ++. It is obvious that the majority of the pre-eclamptic patients have a systolic blood pressure under 180, abnormal gain in weight per week, and a marked edema. The majority of the vascular-renal and hypertension groups have a systolic blood pressure which is over 180. Eighty-six per cent of the hypertension group, 73 per cent of the vascular-renal group, but only 34 per cent of the pre-eclamptic group had no or only + edema. No patients with essential hypertension had marked edema and none gained more than 0.8 kilos per week. It is evident that this group differs from the pre-eclamptic in that the majority of the patients have a much higher blood pressure, comparatively few have edema, and the weight gain is within normal limits.

The hypertension of pre-eclampsia differs from that of the other two groups in several ways. First, there is a difference in degree. Second, patients with pre-eclampsia give little or no increase in blood pressure to the "cold test" but do give a marked response to the injection of pituitrin. Patients of the other two groups usually give a marked response to the "cold test" and none to pituitrin. There has also been the report by Allen and Adson of a patient who had had a sympathectomy for an essential hypertension, subsequently became pregnant and again developed a hypertension which subsided when the pregnancy was terminated. This phenomenon seems to indicate that the hypertension associated with pre-eclampsia is humoral rather than nervous in origin.

The diastolic pressure shows marked variations but on the whole the systolic is a more sensitive indicator of approaching toxemia. Simon made a similar observation, stating that in one-fourth of his patients with toxemia the increase of the systolic blood pressure antedates the appearance of proteinuria or edema by from one to twelve weeks.

We have had six patients with an essential hypertension in whom the blood pressure was lower during pregnancy than it was either ante partum or post partum. It must be remembered that the hypertension is merely a sign of an abnormal cardiovascular-renal system and that the same disease is present with a blood pressure of 160/90 as with one of 210/140. Therefore, the hypertension is just as significant in the patient with the low blood pressure as in the one with the high. As a matter of fact, it is even more important because the duration of the disease has usually been shorter. Consequently adequate treatment may give a greater life expectancy than in the case of the patient with the very high blood pressure.

We have also had two families, in each of which two sisters had an essential hypertension which apparently had its onset in pregnancy. Unfortunately, there were no records of the blood pressure before the pregnancy. This familial tendency to hypertension is well known, but the onset in two sisters in pregnancy is rare and should be investigated further, especially in identical twins.

The appearance of the characteristic cerebral, visual, gastrointestinal, and renal symptoms in a toxemic patient always suggests that con-

vulsions are imminent. Only a few of the patients in the mild group had symptoms. This is to be expected because one of our criteria for a severe case was the occurrence of symptoms. Table I illustrates the fre-

TABLE I. OCCURRENCE OF VARIOUS GROUPS OF SIGNS AND SYMPTOMS, PER CENT*

	MILD			SEVERE		
	PRE-ECLAMPSIA	VASCULAR-RENAL	HYPER-TENSION	PRE-ECLAMPSIA	VASCULAR-RENAL	HYPER-TENSION
H, P, E, and S	4	3	1	46	33	18
H, P, and E	45	38	13	31	24	23
H and P	17	31	39	5	19	25
H and E	17	10	8	5	1	4
H, P, and S				4	11	11
H	6	10	38		5	11
H, E, and S					3	
H and S			1		2	8
P and E	10	6		9	2	
Miscellaneous but no hypertension	1	2				

*H, Hypertension. P, Proteinuria. E, Edema. S, Cerebral, visual, gastrointestinal, or renal symptoms.

quency of symptoms in combination with the other signs. Since they were always associated with a hypertension, it is logical to assume that the symptoms are most likely due to a vascular spasm, resulting in tissue anoxemia or edema, or perhaps both.

It is noteworthy that a hypertension was the most frequent sign, occurring in 90 per cent of the patients. We have always stressed the point that the blood pressure must be individualized. For example, if a patient with a normal systolic pressure of 90 showed an increase of 35 mm. during pregnancy, this would be a hypertension for her. If we had these data available, we believe that almost all of our patients would have had either a relative or absolute hypertension.

Data as to the time of onset of the toxemia are of interest. Pre-eclampsia did not occur before twenty weeks' gestation and only 14 per cent of the patients had it before thirty weeks. In the other two groups 14 per cent of the patients in each group had the disease before the twentieth week and 42 per cent had it before the thirtieth week. Thirty-seven per cent of the pre-eclamptic patients had signs of toxemia before the thirty-sixth week as compared with 66 per cent of the vascular-renal group. Thus, "toxemia" in the first thirty weeks of pregnancy is almost always vascular-renal disease, essential hypertension, or acute glomerulonephritis. Our data demonstrate the well known fact that pre-eclampsia is a disease of the last trimester of pregnancy.

Only 7 per cent of the pre-eclamptic group were delivered before the thirty-sixth week in contrast to the other groups in which 22 per cent and 16 per cent were delivered before thirty-six weeks. Fourteen per cent of the severe pre-eclamptic and 43 per cent of the severe vascular-renal and essential hypertension groups were terminated before thirty-six weeks' gestation.

Ophthalmoscopic examination, even though made by an experienced ophthalmologist, has been of little aid to us in either diagnosis or prog-

nosis. Abnormal changes in the vessels of the retina were described in 35 per cent of the mild pre-eclampsics, 51 per cent of the mild vascular-renal group, and 5 per cent of the mild essential hypertension group. More extensive findings were reported in 47 per cent of the severe pre-eclampsics, 77 per cent of the severe vascular-renal group, and 39 per cent of the hypertensive group. The lesions in the patients with pre-eclampsia have always disappeared by the end of two weeks, in contrast with the retinal changes in the other groups which are permanent.

Stander, Herriek, Adair, and other investigators have made similar observations as to age, parity, blood pressure, etc., but so far as we know, no one has been able in as large a series as ours to demonstrate such marked differences between the various groups.

The following findings, previously reported by us, were also noted in the patients comprising this study: chemical changes in the blood, such as lower hemoglobin, cell volume and serum protein concentration in the pre-eclamptic group than in the other groups; marked decreases in the concentration of these constituents after delivery, or clinical improvement in the pre-eclamptic group and little or no change in the other groups.

There is a 15 per cent increase in the blood volume of pre-eclamptic patients and a 30 per cent increase in that of eclamptic patients after delivery. These changes are also associated with clinical improvement without delivery. There is only a 5 per cent increase in the blood volume after the delivery of normal pregnant patients and of those with vascular-renal disease. These differences in blood and plasma volume changes also indicate that all toxemias of pregnancy are not alike.

The mean urea clearance was 60.5 per cent for pre-eclamptic patients and 58.6 per cent in the vascular-renal patients, thus indicating that a large number of these women have no renal impairment. The average volume of urine per hour under test conditions was 41.4 c.c. before delivery and 72 c.c. postpartum in the pre-eclamptic group, and 50.9 c.c. and 73.2 c.c., respectively, for the vascular-renal. Since identical conditions were used for all tests, it is apparent that pregnancy causes a decreased or delayed output of water.

Data from repeat pregnancies are given in Table II. Two hundred ninety-seven deliveries were observed in 137 patients. We have repeatedly noted that the severity of the condition may be different in a subsequent pregnancy. If gestation accelerates hypertensive disease the blood pressure, etc., should reach a higher level with each pregnancy. This usually occurs and the patients are therefore always advised to have a resection of a portion of the Fallopian tubes. Those who become pregnant again have usually refused or have not been offered contraceptive advice or sterilization. Furthermore, our method for determining the degree of severity is a crude one. It is easily possible for the pathologic process to have advanced and yet our determinations of blood pressure, renal function, ophthalmoscopic examination, etc., show no change. In addition to the group of vascular-renal and hypertensive patients, 66 normal pregnancies occurred in 58 patients whom we had

TABLE II. REPEAT PREGNANCIES WITH TWO OR MORE DELIVERIES IN OUR CLINIC

	NO. OF PATIENTS	NO. OF SUBSEQUENT TOXEMIC PREGNANCIES
Vascular-renal disease:		
Mild	56	68
Severe	10	8
Total	66	76
Essential hypertension:		
Mild	7	7
Severe	1	1
		NO. OF SUBSEQUENT NORMAL PREGNANCIES
Pre-eclampsia:		
Mild	51	
Severe	7	
Total	58	66

REPEAT PREGNANCIES WITH ONE OR MORE DELIVERIES IN OUR CLINIC

	NO. CASES	PRESENT PREGNANCY	
		NORMAL %	TOXEMIA %
Previous history of eclampsia	44	32	68
Previous history of toxemia	218	25	75
Total	262	26	74
Previous normal pregnancy	85		100

previously treated for pre-eclampsia. These patients were watched more closely than usual in the subsequent pregnancy as regards weight gain, blood pressure, and proteinuria, but the pregnancies were normal in all respects. It is possible that the toxemia might have recurred if the patients had not been given special prenatal care. An additional small group of patients is of interest. Five women were observed in 10 normal pregnancies and then each of these in a subsequent pregnancy developed pre-eclampsia. Three were classified as mild and two as severe. In view of these series of patients with pre-eclampsia which was followed by normal pregnancy and normal pregnancy followed by pre-eclampsia, it is difficult to believe that these patients have an inherited tendency to toxemia or that they have a renal or vascular system which has either suddenly become unable to carry the load of pregnancy or suddenly returned to normal. It is also difficult to believe that the toxemia had been caused by a pyelitis or pyelonephritis which was either completely cured in one series or suddenly developed in a second group. It seems to us that we must consider pre-eclampsia an entity distinct from vascular-renal disease and essential hypertension.

We think that the cases reported in this table alone demonstrate that there are at least two large groups of so-called toxemias of pregnancy. The patient with pre-eclampsia recovers completely and has no persistence of hypertension, edema, or proteinuria between pregnancies or recurrence in subsequent ones. The patient with essential hypertension or vascular-renal disease almost invariably has an abnormal

blood pressure or proteinuria between pregnancies and a definite exacerbation in subsequent pregnancies. It is interesting to note that only one-fourth of the patients with toxemia were normal in subsequent pregnancies. This figure should be much larger, because undoubtedly many patients with a history of toxemia were not referred to the toxemia clinic if the pregnancy under observation was normal. The very fact that a certain percentage of patients had no residual pathology and had no recurrence in subsequent pregnancies indicates that the toxemia of pregnancy itself is probably not the cause of a persistent hypertension. Furthermore, 85 of our patients who had toxemia gave a history of a previously normal pregnancy. This would seem to indicate that other factors, such as age, diet, weight, habits, climate, etc., were the predisposing factors rather than an inherent tendency or weakness of the vascular-renal system.

Table III lists pertinent data about the fetus. In most instances fractions have been dropped.

TABLE III. FETAL RESULTS, PER CENT

	MILD			SEVERE			TOTAL
	PRE-ECLAMP-SIA	VASCU-LAR RENAL DISEASE	ESSEN-TIAL HYPER-TENSION	PRE-ECLAMP-SIA	VASCU-LAR RENAL DISEASE	ESSEN-TIAL HYPER-TENSION	
<i>A. Fetal Mortality</i>							
Alive	94	88	94	88	63	79	87
Dead	6	12	6	12	37	21	13
Induced dead	3	7	4	10	32	10	8
<i>B. Induction of Labor and Termination of Pregnancy</i>							
Total induced	26	36	21	56	67	52	36
Per cent of induced dead	10	21	21	18	49	20	24
<i>C. Weight of Dead Fetuses</i>							
Less than 1,000 gm.	0.6	4	0	4	17	4	4
Less than 2,000 gm.	1.4	6	0	11	25	24	7
Less than 3,000 gm.	2.0	8	0	13	30	24	8
<i>D. Weight of All Babies</i>							
Less than 1,000 gm.	1.4	6	0	11	25	24	7
Less than 2,000 gm.	5.0	10	1	18	37	28	11
Less than 3,000 gm.	34.0	33	29	60	70	69	44

"Dead" in Part A includes all unintentional and therapeutic abortions, pre-viable, premature, macerated, stillborn, monstrosities, and neonatal deaths. In other words, if the patient did not have a baby living at two weeks post partum, the fetus was considered dead. This concept of reporting fetal mortality is at variance with the usually accepted method of eliminating abortions, fetuses which are pre-viable or macerated, and monstrosities. We believe that vascular-renal disease frequently and essential hypertension less frequently may be the cause of abortions, premature labor, and intrauterine death of the fetus, and that the seriousness of these various toxemic conditions can best be demonstrated by the use of uncorrected figures. Our data, Part A, indicate that the fetal mortality of the mild vascular-renal group is double that of the pre-eclamptic group. Twelve per cent of the fetuses in severe pre-eclampsia were dead, as compared with 21 per cent dead in the essential hyper-

tension and 37 per cent dead in the vascular-renal groups. These figures confirm our belief in our method of reporting fetal mortality for toxemic patients. It is of the greatest importance to the patient and to the doctor to know that if the diagnosis is severe toxemia, over one-fifth of the pregnancies will not terminate with a live baby. It must be remembered that the patient consults her doctor not for a diagnosis but for a live baby. The "induced dead" means that that percentage of the dead resulted from a termination of the pregnancy by therapeutic abortion or induction of labor. It is striking in the severe group that the major portion of the deaths, 10 per cent out of 12 per cent for pre-eclampsia and 32 out of 37 per cent for vascular-renal disease, occurred where the pregnancy was interrupted.

Part B lists data concerning the interruption of pregnancy. All therapeutic abortions are included. The percentage of induced dead means that that percentage of the total number of patients induced left the hospital without living babies. Fifty-six per cent of the patients with severe pre-eclampsia had the pregnancy interrupted, and 18 per cent of the fetuses were lost. Pregnancy was interrupted in 67 per cent of the patients with severe vascular-renal disease, and 49 per cent of these fetuses were lost. There must be a difference between two conditions.

Part C lists the weights of the dead fetuses. These figures are interchangeable with those of Part A, and one can easily determine the number of previable fetuses. For example, the fetal mortality for the severe vascular-renal group is 37 per cent but 17 per cent of these dead fetuses weigh less than 1,000 gm. Therefore, a corrected fetal mortality would be 20 per cent. This figure can be lowered still more by deleting those cases where the fetus was macerated or died because of congenital abnormalities. However, we are not concerned with corrected statistics but with live fetuses or successful pregnancies. The severe group demonstrates beyond doubt that toxemia is associated with small babies. We are cognizant of the fact that over one-half of these pregnancies were terminated prematurely, which would result in a higher percentage of small babies than normal, but again we must stress the fact that these pregnancies were interrupted in the interest of both the mother and unborn fetus. If delivery had not been forced when it was, many of the fetuses would undoubtedly have been born within a few days or a week without material change in weight and some would have been stillborn.

Part D lists the weight of all babies. Approximately two-thirds of all patients with severe toxemia have babies which weigh less than 3,000 gm. Thirty-seven per cent of those with severe vascular-renal disease have babies weighing less than 2,000 gm. Even though many of these small babies are perhaps more immature than premature, yet the probabilities of the mother having a live baby on discharge from the hospital must be carefully considered.

There have been 16 maternal deaths, of which we know, occurring over a period of seven years. One pre-eclamptic patient died as the result of a gall bladder operation three months post partum, and another died from puerperal infection. The remaining deaths all occurred in patients with vascular-renal disease. Cardiac failure was the cause of death in 4 patients, 3 during the early puerperium, and 1 within one year post partum, and a contributory factor in another death. Cerebral hemorrhage caused death in 3 patients, 1 within one year and the others over two years after delivery. Six deaths were due to uremia, 1 within two months and the other 5 within two years. Two of the latter were due to destruction of kidney tissue by pyelonephritis, but the clinical picture of hypertension, renal impairment, etc., was identical with that seen in vascular-renal disease caused by hypertensive arterial disease. Two other patients died within two years of uremia due to chronic glomerulonephritis. One death was caused by acute glomerulonephritis. Our immediate maternal mortality is 4 or 0.36 per cent. The total known death rate over a period of years amounts to 1.3 per cent. It is

obvious that the cause of death in the majority of our patients was similar to that reported for vascular-renal disease in the nonpregnant; namely, cerebral hemorrhage, cardiac failure, or uremia. Autopsies were performed on 64 per cent of our patients and confirmed our clinical observations. The pathologist was unable to decide in one case as to the etiology of the renal lesions, that is, whether they were caused by a glomerulonephritis or a nephrosclerosis or both.

During the period from 1931 to 1937 we have had over 1,200 toxemic deliveries, an incidence of 7.5 per cent. They have been classified, using criteria previously described as follows: pre-eclampsia total 47.4 per cent (mild, 25.7 per cent; moderate, 15 per cent; severe, 6.7 per cent); vascular-renal disease total 35.8 per cent (mild, 12.5 per cent; moderate, 11.3 per cent; severe, 12 per cent); essential hypertension total 12 per cent (mild, 6.2 per cent; moderate, 3.4 per cent; severe, 2.4 per cent); eclampsia 4.4 per cent; acute glomerulonephritis 0.5 per cent. Mild in the present paper comprises both the mild and the moderate groups.

Kellogg of the Boston Lying-in Hospital states that 87 per cent of their toxemic patients had pre-eclampsia, 2 per cent eclampsia, and the remainder had disease of the vascular or renal system.

Stander reports the following distribution: low reserve kidney, 61.8 per cent; chronic nephritis, 17.9 per cent; unclassified toxemia, 10 per cent; pre-eclampsia, 7.8 per cent; and eclampsia, 2.5 per cent.

Despite a difference in terminology for these various conditions, there should be a comparatively close agreement for the various groups. Our data cannot be reconciled with Kellogg's report, but they do check in part with Stander's. Our pre-eclamptic patients far outnumber his, but if half of his low reserve group are considered as having mild, or Group 1 pre-eclampsia, which he admits is possible, and the remainder as belonging to the vascular-renal or hypertension group, the figures will check. Kellogg's figures are based on hospital diagnosis. It is the general experience that if the type of toxemia is diagnosed only on the hospital records, many patients will be classified wrongly as pre-eclampsia. Our toxemia clinic has been functioning for almost seven years, and we attempt to follow our patients until they die. This may explain in part the distribution of our cases.

On several occasions the first pregnancy was diagnosed pre-eclampsia, with no evidence of vascular-renal disease after the puerperium. The second pregnancy, however, and in a few cases, subsequent pregnancies also showed a recurrence of the toxemia. The diagnosis, of course, is vascular-renal disease for all pregnancies. There is nothing inconsistent with this diagnosis, as after acute glomerulonephritis the blood pressure and urine may, according to the usual tests, be normal for years and then become abnormal again. Similarly, patients with a labile blood pressure may, under abnormal mental stress or in association with infection, have a hypertension which subsequently subsides, to recur again months or years later and then be permanent.

Essential data for a case of pre-eclampsia are given in Table IV. This patient was selected because we first thought that she had vascular-renal disease in view of her parity and retinal pathology. However, her subsequent course demonstrates that the condition must have been pre-eclampsia.

TABLE IV. BASAL METABOLISM (44575). PRE-ECLAMPSIA

DATE	WEIGHT KILO	EDEMA	PRO- TEIN- URIA	BLOOD PRES- SURE MM.	COMMENTS
1929					First pregnancy, normal
8/19/31	80	0	0	110/ 64	Second pregnancy. Patient 24 yr. old, at term 1/15/32, Hb. 11 gm. %. 9 <i>prenatal visits</i>
10/27/31	86	+	0	110/ 66	Diet instructions
12/ 1/31	89	++	+	138/ 84	
12/29/31	92	+++	+++	160/ 92	Hospital; cerebral and visual symptoms, Hb., 9.1 gm.%; cell volume, 32%; serum protein, 5.7 gm.%; nonprotein nitrogen, 26 mg. %
12/30/31		+++	+++	162/102	Ophthalmoscopic: Acute retinitis, in- travenous 20% glucose in 1,000 c.c. amounts
12/31/31		++++	+++	180/120	Induced labor by R.M. and gauze pack, 2,340 gm. live fetus
2/24/32		0	0	122/ 78	Hb., 6.5 gm. %; cell volume, 27%; se- rum protein 6.2 gm. %; urea clear- ance, 36%
2/22/33	85	0	0	105/ 65	Third pregnancy, at term 9/2/33, Hb. 11.9 gm. %
9/24/33	90	0	0	130/ 90	Spontaneous delivery, 3,970 gm. fetus, 12 <i>prenatal visits</i>
1/16/34	86	0	0	112/ 74	Fourth pregnancy, at term 8/25/34, Hb., 11.5 gm.%; cell volume, 41%
2/13/34	87	0	0	98/ 60	Ophthalmoscopic: Normal. Urea clear- ance, 95%
9/ 4/34		0	0	108/ 70	Hb., 12.7 gm.%; cell volume, 39%; serum protein, 7.4 gm.%; urea clear- ance, 71%
9/12/34	90	0	0	134/100	Spontaneous delivery, 3,285 gm. fetus, 15 <i>prenatal visits</i>
10/21/34	87	0	0	120/ 90	
5/ 9/38	93	0	0	95/ 60	Urea clearance 100%. Hb., 13.4 gm. %; serum protein, 7.2 gm. %

Table V contains data for a patient with essential hypertension which was either of short duration or first manifested itself during pregnancy. The persistently high blood pressure, absence of proteinuria, low normal urea clearance, etc., clearly indicate that the patient had an essential or primary hypertension.

The hypertension which may occur in patients with hyperthyroidism quite often causes confusion. This disease was present in 1.9 per cent of the pre-eclamptic, 1.6 per cent of the vascular-renal, and 7 per cent of the essential hypertension group. Eisele and Ricketts of our Medical Department have stated that the blood pressure remained constant or showed appreciable decreases in many of these patients when treated

TABLE V. ESSENTIAL HYPERTENSION

M. D. (91383), a 23-year-old primipara. Term May 12, 1934. Admitted to hospital on Feb. 25, 1934 because of abruptio placentae. Spontaneous delivery of a 1,100 gm. fetus which lived. On Sept. 4, 1934 when the patient was six weeks pregnant, an abdominal hysterotomy and tubal ligation were performed. Ophthalmoscopic examination: Feb. 28, 1934, normal; Sept. 3, 1934, hypertensive neuroretinitis. In 1936 she had severe epistaxis; blood pressure was 196/130; and there were proteinuria and casts in the urine.

DATE	WEIGHT	BLOOD PRESSURE	ALBUMIN	EDEMA
10/ 5/33	49.5	110/80	0	0
10/28/33	51.1	170/105	0	0
1/ 9/34	54.0	148/114	0	0
1/30/34	55.2	130/110	0	0
2/25/34		210/150	0	0
4/25/34	53.0	150/100	0	0
6/ 5/34	51.8	220/150	0	
9/ 4/34	49.0	194/134	0	
9/28/34	46.2	240/126	0	0

DATE	HEMOGLOBIN GM. %	HEMATOCRIT %	SERUM PROTEIN GM. %	NONPROTEIN NITROGEN MG. %	BLOOD UREA NITROGEN MG. %	UREA CLEARANCE % OF NORMAL
2/26/34	11.8	43	6.3	20	8	51
6/19/34		49	7.2	27	12	52
9/ 3/34	14.0	43		27	13	56

with iodine. The treatment of pre-eclampsia and eclampsia with thyroxin, as suggested by Küstner, is at variance with the above findings. Thyroid therapy has been of no value in the treatment of pre-eclamptic patients.

DISCUSSION

We believe that we have been able to demonstrate that there are several groups of so-called "toxemias of pregnancy," which differ from each other in many ways. Obstetricians have recognized these differences for years, but have failed to agree on a common nomenclature. The term is, unfortunately, an all-inclusive one, and is applied to any pregnant patient who has any of the following symptoms or signs: hypertension, edema, proteinuria, convulsions, vomiting of early or late pregnancy, jaundice, neurologic and mental symptoms, pruritus, dermatitis, etc. Much of the confusion in classification is due to this lack of definition of the term.

"Toxemia of pregnancy" should mean the occurrence of one or more of the following signs in a pregnant woman: hypertension, edema, proteinuria, or convulsions. The term, when possible, should be restricted to pre-eclampsia and eclampsia. All other conditions in pregnancy which are associated with any or all of these signs should be classified as essential hypertension, vascular-renal disease, acute glomerulonephritis, etc.

Whether or not these particular terms are used is immaterial. The point is that further progress will only be possible when everyone doing investigative work is cognizant of the data and knowledge already available.

The proper diagnosis of these conditions is more than academic. The treatment, prognosis, and fetal mortality, and not infrequently, the maternal mortality depend on a proper diagnosis. For example, we hospitalize pre-eclamptic patients when the systolic blood pressure is 160 and quite often even with a lower blood pressure, if the weight gain is excessive, if proteinuria suddenly occurs, or if there is marked edema or symptoms. The patient with essential hypertension or vascular-renal disease is hospitalized only when the systolic blood pressure reaches 190 or more, or if the proteinuria is more than 5 gm. per twenty-four hours. Likewise decreased visual acuity or amaurosis in pre-eclampsia has an excellent prognosis, but in vascular-renal disease there is always some permanent impairment of vision.

We now have over 160 patients whom we have delivered two or more times. These records are valuable, but we should strive to obtain in addition the combined records of a pregnancy and proper follow-up, together with the records from school, insurance, and premarital examinations. Such records would be invaluable and would enable us to settle many of these moot points.

Since we cannot agree on a classification of the toxemias of pregnancy, we should establish a central registry similar to that for cancer and bone tumors where a complete abstract of each case would be sent. After a few years sufficient material would be available to permit proper evaluation of etiology, classification, and treatment.

CONCLUSIONS

The term, "toxemia of pregnancy," should be restricted to those abnormal conditions occurring in pregnancy which are characterized by the occurrence of one or more of the following signs: hypertension, edema, proteinuria, and convulsions. These diseases are: eclampsia, 4.4 per cent; pre-eclampsia, 47 per cent; vascular-renal disease, 36 per cent; essential hypertension, 12 per cent; and acute glomerulonephritis, 0.5 per cent.

Eclampsia and pre-eclampsia are distinct disease entities occurring only in pregnant women. They are most likely to occur during the last trimester in primiparas, whose age is less than thirty and who gain weight too rapidly.

The terms, essential hypertension and vascular-renal disease and pregnancy, as used by us, mean that the primary process in both conditions has been, as a rule, a hypertensive arterial disease. The former condition will ultimately become the latter.

Essential hypertension may be present before or develop during pregnancy. It is also found most frequently in primiparas before the age of thirty, but the weight gain is usually within normal limits, and two-thirds of the patients develop their hypertension before the thirty-fourth week of pregnancy.

Vascular-renal disease is found most frequently in multiparas who are older than thirty and overweight. Two-thirds of these patients also have their signs and symptoms before the thirty-fourth week of gestation. This disease is usually caused by a long-standing essential hypertension, chronic glomerulonephritis, or pyelonephritis.

A systolic blood pressure of 140 mm. or more is the most frequent sign of beginning toxemia, occurring in at least 90 per cent of the "toxemias of pregnancy." The systolic blood pressure in pre-eclampsia is usually less than 180 mm. and rarely over 200. The majority of the patients in the other two conditions have a systolic pressure over 180 and many over 200.

A weight gain of over 0.6 kilos per week is indicative of the possible onset of pre-eclampsia or vascular-renal disease. If this gain is long-continued, subcutaneous edema usually develops.

Proteinuria, unless the twenty-four-hour excretion amounts to 5 gm. or more, is of no significant value for diagnosis or prognosis.

The marked changes in blood and plasma volume, hemoglobin, cell volume, and serum protein concentration that occur in pre-eclampsia, in contrast with vascular-renal disease, also indicate that these are two separate and distinct diseases.

Hypoproteinemia was not a factor in causing toxemia, because the average concentration of the serum protein was 6.2 in pre-eclampsia, 6.7 in eclampsia, and 6.7 gm. per cent in patients with vascular-renal disease.

Toxemia does result in smaller babies. Eleven per cent of all the toxemic babies weighed less than 2,000 gm. and 44 per cent weighed less than 3,000 gm.

The fetal mortality of severe pre-eclampsia is 12 per cent; of severe essential hypertension, 21 per cent; and of severe vascular-renal disease, 37 per cent. The fetal mortality for all cases is 13 per cent.

The major portion of the maternal deaths occurred in the vascular-renal group over a period of years after delivery. They were due to cardiac failure, cerebral hemorrhage, or uremia.

We suggest that an abstract of each case of toxemia be sent to a central registry. Thus, in a short time, sufficient material would be available to permit proper evaluation of etiology, classification, and treatment.

REFERENCES

- Adair, F. L.: AM. J. OBST. & GYNEC. 26: 530, 1933. Allen, E., and Adson, A.: Proc. Staff Meet. Mayo Clin. 12: 726, 1937. Barker, M.: AM. J. OBST. & GYNEC. 35: 949, 1938. Corwin, J., and Herrick, W.: Ibid. 14: 783, 1927. Dieckmann, Wm. J.: Ibid. 32: 227 and 927, 1936. Idem: Proc. Soc. Exper. Biol. & Med. 32: 1127, 1935. Idem: AM. J. OBST. & GYNEC. 26: 543, 1933; 29: 472, 1935. Dieckmann, Wm. J., and Michel, H.: Ibid. 33: 131, 1937. Dieckmann, Wm. J., Michel, H. L., and Woodruff, P. W.: Ibid. 36: 408, 1938. Eisele, W. C., and Ricketts, H. T.: To be published. Harden, B., McElroy, W., and Huggins, R.: AM. J. OBST. & GYNEC. 30: 524, 1935. Herrick, W., and Tillman, A.: Ibid. 31: 832, 1936. Kellogg, F., Smith, J., Teel, H., and Reid, D.: Ibid. 33: 300, 1937. Page, I. H.: Bull. New York Acad. Med. 13: 645, 1937. Simon, L.: Acta obst. et gynec. Scandinav. 11: 365, 1931. Stander, H., and Kuder, K.: AM. J. OBST. & GYNEC. 35: 1, 1938. Stander, H., and Peckham, C.: Ibid. 11: 583, 1926. Stieglitz, E.: Illinois M. J. 50: 234, 1926.

DISCUSSION

DR. JOHN W. HARRIS, MADISON, WIS.—Some fifteen years ago we studied a series of cases of the so-called late toxemias of pregnancy and followed them for at least a year after delivery. In more than one-half of those in whom the diagnosis of pre-eclampsic toxemia and eclampsia had originally been made we found evidences of permanent vascular and renal damage. We were unable to ascertain in most instances whether the original diagnosis was incorrect or whether a primary toxemia of pregnancy had been the causative factor in the production of the permanent damage to the vascular and renal systems. Subsequent studies by other investigators have indicated similar results.

Many attempts, as Dr. Dieckmann has stated, have been made to improve the classification of the late toxemias with varying results, but all of them have left much to be desired. With the patient before us it is often impossible to determine the proper group regardless of the classification one is following. This is not only unfortunate from the standpoint of the welfare of the patient, but the numerous classifications have created a veritable chaos in the literature on the subject. It is often difficult to compare reports of various authors because of the confusion of terms.

The classification which Dr. Dieckmann advocates seems more logical than those that have preceded it, and it certainly is more in accord with modern medical and pathologic concepts. Only time will tell its correctness. However, there still remains the problem of whether those cases thought to be vascular or renal are primary or secondary to a process instituted by pregnancy itself.

Dr. Dieckmann's advocacy of a central toxemia registry deserves serious consideration. Perhaps a large number of case histories submitted by various clinics to a central registry and there thoroughly studied and analyzed might well be of real value in improving the classification of these complications, as well as shedding additional light on their proper treatment.

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—Dr. Dieckmann apparently believes that eclampsia and pre-eclampsia play no role in the production of chronic hypertension. This is at variance with our experience, since about one-third of our cases of pre-eclampsia and eclampsia show hypertension a year later. The reason for this discrepancy lies, I believe, in the fact that Dr. Dieckmann distinguishes between the acute and chronic varieties of hypertension entirely on the basis of his findings six weeks post partum.

For instance, if a patient in the last month of pregnancy develops sudden hypertension, albuminuria, and edema, and all these signs have disappeared at the six-weeks return visit, the case is called by him pre-eclampsia. If, however, the hypertension, let us say, has not disappeared, the case is classified as essential hypertension. She may well have had essential hypertension at the six-weeks return visit but the pertinent question is: what did she have during the last month of pregnancy? It is my feeling that she had pre-eclampsia which resulted in chronic hypertension.

Now let us suppose on the other hand that the condition of this hypothetical case became worse prior to delivery and convulsions supervened. Then if she showed hypertension six weeks post partum, we would not classify the case as essential hypertension, but would say that she had eclampsia which resulted in chronic hypertension.

I realize that the tendency to classify the toxemias some weeks post partum is rather general, but this practice overlooks entirely the fact that the chronic hypertension seen at the six-weeks return visit may be the result of the acute toxemia sustained during the last month of pregnancy.

Just as chronic hypertension represents a chronic vascular process, we believe that the acute toxemias represent an acute vascular process in the form of a vessel spasm which, if allowed to continue for several weeks or so, results in permanent structural injury to the vessel wall, arteriolosclerosis and consequent hypertension. This question is of great practical importance since it obviously has a bearing on the optimum time to terminate pregnancy in cases of pre-eclampsia.

While I disagree with Dr. Dieckmann on the point mentioned, I feel that otherwise his conception of the several varieties of hypertension of pregnancy is sound. His emphasis on the chronic hypertensive states, essential hypertension and vascular-renal disease, as he calls them, is particularly timely. To us, this group is a more difficult one to treat, particularly if the patient is a primigravida anxious for a baby, and is a more important cause of death, both maternal and fetal, than are the acute toxemias, eclampsia, and pre-eclampsia.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—In considering the so-called nephritic toxemias of pregnancy, it has always been my understanding that the kidney impairment is due to arterial damage sufficient to put out of commission a certain number of glomeruli and bring about finally a kidney functioning like one with chronic glomerular nephritis. If kidney function tests show any great impairment the chances for the fetus are comparatively bad, and it is now our practice to terminate these cases early in pregnancy when they occur.

Dr. Dieckmann has emphasized the group of essential hypertension. Now I wonder whether an essential hypertension so-called, with normal kidney function tests, will have the same effects as do the cases of true nephritic toxemias. Recently I have followed through pregnancy a case of essential hypertension, well known to be such, in a nulliparous woman in whom the blood pressure was 180 systolic. This did not vary at all through pregnancy and her kidney tests were normal throughout. Another case was observed in which the outcome was very favorable and in which even the blood pressure dropped during pregnancy, to rise again subsequently. In treating these cases I believe that until further evidence is gathered, the more conservative attitude should be taken with these cases of so-called essential hypertension.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—When I came to the Sloane Hospital, now nearly twelve years ago, I found that Dr. Herrick, under the late Dr. Studdiford, had been making a study of the cases of late toxemia. Very soon after that Herrick began classifying these cases, just as Dr. Dieckmann has done today, into essential hypertensions, nephrities, and pre-eclampsies. All of us associated with Dr. Herrick have become more and more certain that his is a workable classification.

As has been said, it is not always possible to classify the case when first seen, or even for sometime afterward, but the very long follow-up which Herrick has now had has convinced him that the great majority are primarily vascular cases. The first lesion is a vascular one and this may be followed by kidney complications as the vessels of the kidney become affected. Practically all autopsies which have been obtained on women dying after exhibiting those symptoms during a pregnancy have shown vascular lesions. So we have been convinced for a great many years now that this classification which Dr. Dieckmann has given us tonight is the most workable one we have been able to get so far.

DR. FRED L. ADAIR, CHICAGO, ILL.—I approve very heartily of Dr. Dieckmann's classification. In 1923 I grouped the cases of hypertension during pregnancy into four main groups, recognizing, however, that there was no fundamental difference between pre-eclampsia and eclampsia. The eclamptic and the pre-eclamptic group showed the usual rises in blood pressure which dropped almost to normal, but in certain cases it persisted after delivery. There was one rather unusual group of hypertension, with a pre-existing high blood pressure which showed no increase during pregnancy. Then there was another group with pre-existing hypertension with a superimposed pre-eclamptic hypertension.

Certain case histories illustrate these differences. The first patient was seen in early pregnancy with a history of eclampsia in a previous pregnancy. She was observed in the fourth month of the second pregnancy with a hypertension which then gradually rose, fell after delivery, and then after six months rose again. Her blood pressure continued high for some time but gradually dropped to a pressure somewhat higher than in early pregnancy and continued over a period of years at this level. The patient is still living.

The second case is that of a woman who died about four years from the time she was first seen. She came to me in April, 1916 in early pregnancy with hypertension which rose to a high level. The fetus died and the pregnancy was terminated. She became pregnant again later when the blood pressure rose to a higher level than in the preceding pregnancy, and a dead pre-viable fetus was delivered. Following this the systolic pressure rose but the diastolic did not change much. Subsequently she went from bad to worse and died in November, 1919, almost four years after I first saw her. A complete autopsy was not obtained, but we did get the kidneys. The vessels showed marked changes and the case was diagnosed as an arteriolar nephritis.

I believe there is enough evidence at least to justify the classification of pre-eclampsia and eclampsia as being probably the true toxemias of pregnancy. There is no reason why such patients may not have had some preceding vascular disease. These latter conditions may occur independently of pregnancy, but pre-eclampsia and eclampsia are doubtless due to the same cause and one associated with pregnancy.

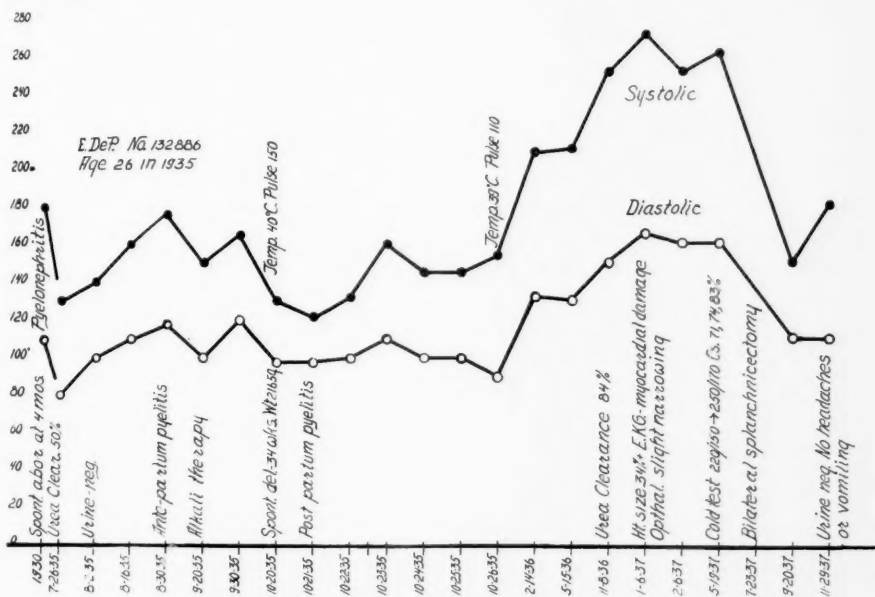


Fig. 1.—E. D., No. 132,886. Patient with essential hypertension, but blood pressure was still labile and did not increase during pregnancy. Marked rise in pressure within one year after delivery, relieved by bilateral splanchnicectomy.

DR. DIECKMANN (closing).—Dr. Eastman has raised a question regarding the possibility of permanent damage to the vascular-renal system from eclampsia or pre-eclampsia. Our opinion is not a fixed one, but it seems that a more rational explanation for the presence of hypertension and/or proteinuria one year post partum is that a hypertensive arterial disease was either present before the pregnancy or appeared in a pregnant woman with a predisposition to it. Furthermore, it is not inconceivable that pre-eclampsia and eclampsia might occur in a patient with vascular-renal disease.

Dr. Eastman postulates a patient who at thirty-six weeks begins to have signs of toxemia and who has hypertension when seen one year post partum. I think it highly improbable that this could occur and believe that if the patient had been properly observed during her pregnancy some evidence of an abnormal vascular-renal system would have been noted.

We agree with Dr. Schwarz that, if on *repeated tests* there is obvious renal impairment, the pregnancy should be terminated. He mentions one patient with essential hypertension who had no increase in blood pressure during her pregnancy. We have had six similar patients of whom we know. These cases are rare because, as a rule, the hypertensive symptoms and signs are intensified. The accompanying chart gives an excellent example of a patient with a very labile blood pressure which did not increase during pregnancy, even when an acute pyelitis occurred. Within a year, however, the blood pressure was so high and the associated symptoms so marked that the patient had a bilateral splanchnicectomy.

Dr. Watson has mentioned Herrick's work. We are familiar with it because he is one of the pioneers. This classification is not original with us but is commonly used by the internist.

A STUDY OF THE LYMPH GLANDS IN CANCER OF THE CERVIX AND CANCER OF THE VULVA*

FRED J. TAUSSIG, M.D., ST. LOUIS, MO.

(From the Barnard Free Skin and Cancer Hospital)

THE spread of cancer of the female genital tract through the tributary pelvic lymphatics was actively investigated in the early years of the present century. Since that time there have been relatively few pathologic studies of this question. Special interest of long standing in the operative removal of lymph glands for certain forms of pelvic carcinoma has enabled me to accumulate considerable material for histologic study. It is the analysis of this material that forms the basis of the present study. Since the number of cases of cancer of the vagina, of the uterine body and of the ovary, in which glands were removed was too small, consideration has been limited to those in which the primary site was in either the vulva or the cervix.

A total of 1,271 lymph glands were subjected to microscopic examination. In the group of cervix cancers, 521 glands were removed, 502 by operation and 19 at autopsy. The 750 glands associated with cancer of the vulva were all removed by operation. The types of operation done in these cases were:

Gland removal with hysterectomy for cervix carcinoma	2 cases
Iliac lymphadenectomy for Group II cervix carcinoma	83 cases
Iliac lymphadenectomy for Group III cervix carcinoma	7 cases
Double-sided Basset gland removal for vulva carcinoma	53 cases
One-sided Basset or incomplete gland removal for vulva carcinoma	12 cases
Autopsy for cervix carcinoma	9 cases

With the exception of the inguinofemoral lymph chain which was excised en masse, each gland was removed separately, and placed in a bottle, labeled as to side and location. In many cases a photographic record of the gross appearance of these glands, size, and location was made shortly after operation. In the vulvar cases the primary tumor was photographed with the glands (Fig. 1). In the cervix cancers, the tubes and ovaries removed at the time of the iliac gland resection were included in the picture (Fig. 2). In this way it was possible to record information concerning the anatomic distribution of cancer metastases in these two groups of tumors and also obtain data concerning the varying histopathology in different groups of pelvic lymph glands. Such systematic studies of glands have not to my knowledge been heretofore made on a large scale.

Our knowledge of the anatomic distribution of the pelvic lymph glands in women has been largely based on careful dissections of the cadaver, at times associated with the injection of some coloring material to outline more clearly the path of the lymph channels and the correlation of the various groups of lymph glands. A study of the numerous

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

contributions on this subject found in textbooks of anatomy leave the reader with a rather confused picture of the myriad glands and channels by which lymphatic drainage takes place. In the course of the 157

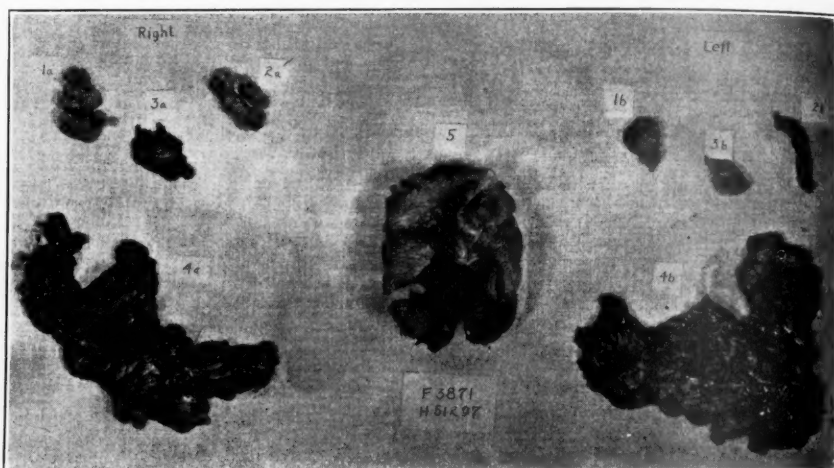


Fig. 1.—Carcinoma of the vulva. Basset operative removal of lymph glands with vulvectomy. Anatomic distribution of excised material: vulva in center; inguino-femoral lymph gland mass with round ligaments below, left and right side; external iliac and obturator glands above, left and right side.

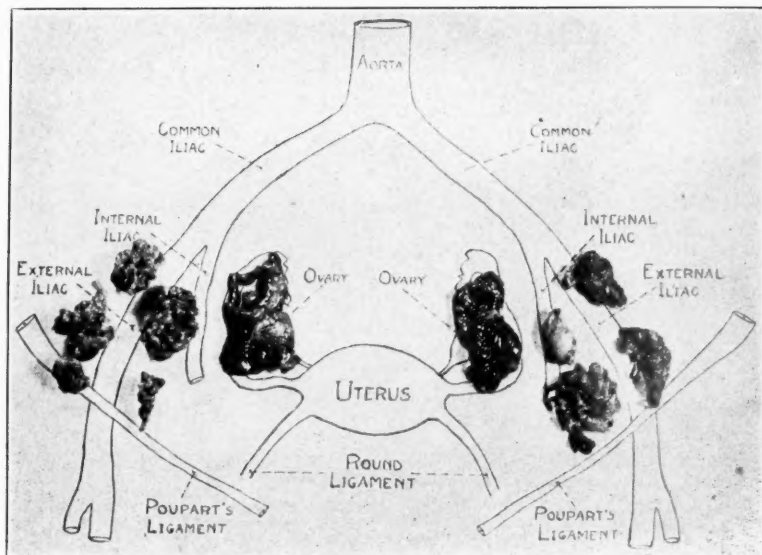


Fig. 2.—Carcinoma of cervix (Group II). Iliac lymphadenectomy with removal of adnexa. Anatomic distribution of excised material. Tubes and ovaries and lymph glands placed on diagrammatic sketch as found at operation.

operations in which I made extensive dissections of the lymphatic chains involved in cancer of the vulva and cancer of the cervix I became convinced that, while there was some variation in the anatomic location of the lymph glands, the total number of these glands was not nearly as

great as has been usually described. My operations did not go so far as to include the sacral glands, situated lateral to the rectum on a level with the sacrouterine ligaments, or the higher common iliac and periaortic glands situated near the sacral promontory. They were limited essentially to the five groups described below:

1. *The Inguinofemoral Lymph Chain.*—From six to twelve glands, occasionally more, were imbedded in the fat and fascia extending parallel to and usually slightly below Poupart's ligament. Along the saphenous veins they were found as low as two to three inches below the femoral ring and several were located in the loose fat of Scarpa's triangle. One or two glands were usually situated in the fascial tissues of the fossa ovalis and almost invariably one gland was pocketed just below the femoral ring, internal and slightly posterior to the femoral vein. This last-named gland, the gland of Cloquet or Rosenmueller, was commonly the site of carcinomatous metastasis. Up to eight years ago, I followed Basset's original technique and cut Poupart's ligament to gain access to this gland, but wider experience convinced me that this was rarely necessary, since with a little care, the gland could be removed completely without risk of injuring the femoral vein, leaving Poupart's ligament intact and thus simplifying the operation.

2. *The External Iliac Glands.*—In every case of vulvar carcinoma and in the majority of cervix cases one or two glands were removed from the iliac fossa external to, and occasionally superimposed on, the external iliac artery just above Poupart's ligament. This gland was invariably imbedded in a considerable mass of loose fat, was rather large, from $1\frac{1}{2}$ to 4 cm. in diameter, soft in consistency, with a definite fibrous capsule. On section it usually consisted largely of fat with a narrow rim of lymphatic tissue.

3. *The Obturator Glands.*—The obturator gland was situated usually about 1 cm. below the external iliac vein running parallel to and often closely attached to the obturator nerve for a distance of 3 or 4 cm. This gland was as a rule rather firm in consistency, long and narrow, with rounded contour. Occasionally a second gland occurred in this location. In fatty individuals it was imbedded in a mass of loose fat adjacent to the obturator nerve. Its upper margin lay close to the origin of the uterine artery and its lower margin just above the femoral ring.

4. *The Hypogastric Glands.*—There was considerable variation in the location of the hypogastric glands. They were usually pocketed in the angle between the external and internal arteries, readily exposed when the broad ligament had been widely opened. Occasionally however they were tucked behind the external iliac vein near its junction with the internal iliac vein. Exceptionally we have found them over the dividing point of the two arteries or between the psoas muscle and the external iliac artery near this junction. There was usually one distinct, rather firm, irregularly ovoid gland, 2 cm. in diameter but, in about one-fourth of the cases one or two additional nodes were found. Technically they were the most difficult to remove, because of their proximity to the large vessels, and the frequency of dense adhesions to these structures. The ureter runs over them but can be pushed aside since it clings to the posterior peritoneal sheath. Cancer metastasis was the most common cause of these adhesions; but in several instances hard, apparently malignant glands were excised with difficulty, only to find on microscopic section that they showed fibrosis but no evidence of carcinoma. In all these cases the patient had received a full course of x-ray therapy before operation and the thought arose that the adhesions may have been due to sclerosis following radiation of a malignant metastasis. In 4 cases adhesions were so dense that a section of the external iliac vein (3 times) or artery (1 time) had to be removed with the gland. In none of these cases did any complicating disturbance of circulation result.

5. *Ureteral Glands.*—In 1903 Sampson called attention to the frequency of microscopic lymph nodes in the broad ligament near the crossing of the ureter and uterine vessels. Occasionally these nodes were larger, up to 1 cm. in diameter, and, especially in cancerous invasion of the cervicovesical septum, it was not unusual to find the

ureteral gland, also called the gland of Championnier, involved by metastasis. Its removal was by no means simple, at times requiring ligation of the uterine vessels and in one case resection of an adherent portion of the uterine vein. Where this portion of the broad ligament was sclerosed or evidently carcinomatous, no attempt was made to isolate the ureteral gland. Where, however, a careful digital palpation of this area revealed a circumscribed nodule, it was excised.

Out of the total of 1,271 lymph glands removed, the anatomic distribution was as follows: inguinofemoral chain, approximately 540 glands, external iliac glands 212; obturator glands 259; hypogastric glands 253; ureteral glands 7.

In 864 of the 1,271 glands microscopic sections were available for careful histologic study; 483 of these glands were associated with cervix cancer and 381 were in cases of cancer of the vulva. The question of

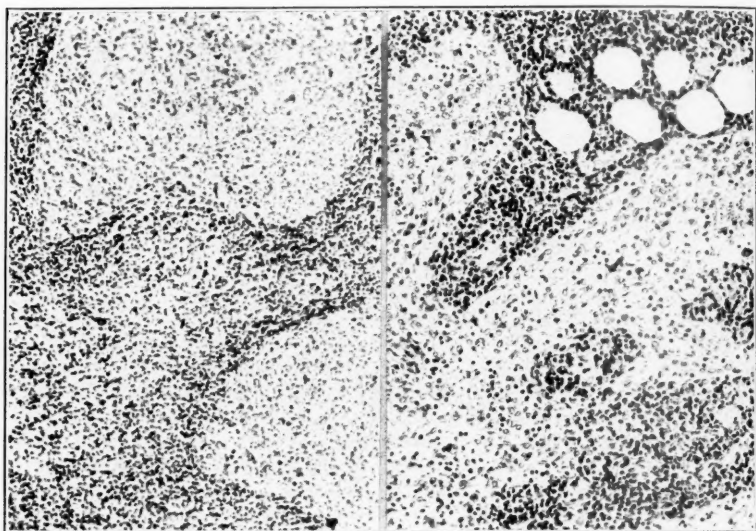


Fig. 3.

Fig. 4.

Fig. 3.—Hyperplasia of the follicles. Unusual proliferation of the germinal centers, almost simulating a metastasis.

Fig. 4.—Endothelial hyperplasia. Active growth in the elements comprising the reticuloendothelial system including many macrophages.

what is normal and what is pathologic in the histologic structure of lymph glands is one that is far from settled. Pathologists have a tendency to call glands hyperplastic when they might well be looked upon as normal. The size of lymph glands varies greatly in different individuals and in different anatomic locations. Age and obesity play an important role in the normal histologic picture. In attempting to group glands according to the dominant characteristics found, I confess great difficulty in attempting to differentiate between these normal variations and those due to associated pathologic conditions, infection, or carcinoma.

Almost every conceivable variety of lymph gland pathology was to be found in the 864 glands that were reviewed in this study. I attempted in each case to classify the gland according to the dominant

histologic characteristic. In two cases all the glands removed showed the typical picture of a tuberculosis. One was associated with cancer of the vulva and one with a cervix cancer. In the remaining cases I grouped them under follicular hyperplasia (Fig. 3), endothelial hyperplasia (Fig. 4), hyaline degeneration (Fig. 5), fibrous fatty, diffusely cellular, and calcified (Fig. 6). Some difference was noted between the vulvar and the cervix cases as shown in Table I. It will be noted that endothelial hyperplasia was more common in the cervix cases, while follicular hyperplasia and fibrous-fatty changes were noted relatively more frequently in the vulva carcinomas. Since the atrophic changes associated with fibrous and fatty infiltration are characteristic of old age, this difference may be due to this fact, for in cervix cases the average age was about 42 years, whereas in vulvar cancer it was 59 years.

It has been stated by A. M. Welsh and others that radiation treatment produces a destruction of the lymph follicles and this would seem

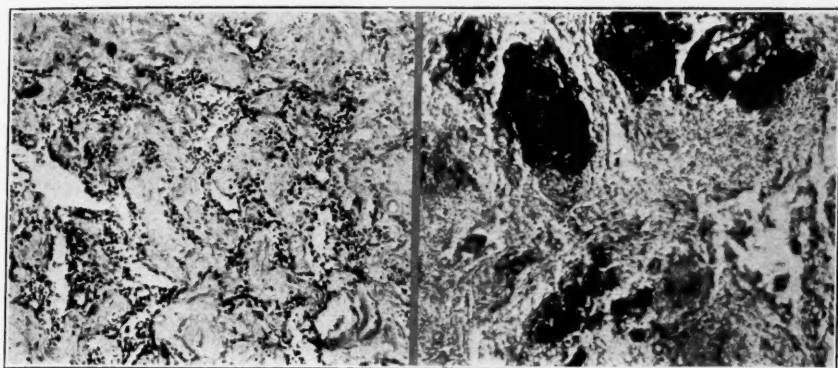


Fig. 5.

Fig. 6.

Fig. 5.—Hyaline degeneration of lymph glands with marked destruction of normal follicles and reticulum, possibly attributable in part to the products of cancer metabolism.

Fig. 6.—Calcification of lymph glands, often a sequel to hyaline changes.

to be confirmed by my observations. In the cervix cases the operative gland removal for the first three years (1930-1934) was usually not preceded by any radiation. In the following two years (1934-1936) the radiation dosage averaged only about 2,400 r. units. In the last two years (1936-38), preliminary radiation was very heavy, averaging 5,600 r. units, and at times associated with a radium dose of 4,500 mg. hr. The

TABLE I

PRIMARY TUMOR	FOLLICULAR	ENDOTHELIAL	HYALINE	FATTY FIBROUS	DIFFUSELY CELLULAR	CALCIFIED	TOTAL
Cervix	96	120	84	137	30	16	483
Vulva	91	62	63	140	10	15	381

glands were divided into two groups: those that showed definite follicles and those that did not show any such germinal centers. In these three periods of my operative experience, there were marked differences (Table II).

TABLE II

YEARS	FOLLICLES PRESENT	FOLLICLES ABSENT	PER CENT FOLLICLES PRESENT
October, 1930—May, 1934	60	18	77
May, 1934—May, 1936	37	56	40
May, 1936—May, 1938	75	212	26

The marked difference between 77 per cent with follicles in the early group and only 26 per cent with follicles in the last group showed without reasonable doubt that heavy radiation produces marked destruction of the germinal centers. What bearing this may have on the growth or spread of the disease is a matter for debate. On the one hand the lymphocytes are probably an important aid in fighting off the invasion of this disease but on the other hand the sclerosing effect of such treatment on the tributary lymph channels and glands may tend to block its spread to other portions of the body.

In the cervix cases a division of the histologic characteristics according to the three principal locations showed the following interesting differences.

TABLE III

LOCATION	FOLLICULAR	ENDOTHELIAL	HYALINE	FATTY FIBROUS	DIFFUSELY CELLULAR	CALCIFIED	TOTAL
Hypogastric	69	50	34	35	18	1	207
Obturator	23	54	33	49	5	7	171
External iliac	4	16	15	53	4	8	100

The hypogastric glands showed follicular hyperplasia most frequently; the obturator glands were characterized by endothelial hyperplasia with a considerable percentage of fatty fibrous changes, whereas the external iliac glands situated in the loose fat of the iliac fossa were predominantly of the fatty type with fibrous capsule and septa. In many of these fossa glands, there was only a tiny crescent of lymphatic cells and a thin fibrous capsule enclosing a mass of fat.

According to C. Sternberg hyaline degeneration is characteristic of lymph glands in cases of malignant disease. While we had no basis for comparison with normal cases, it was rather striking that in 84 of the cervix cancers and 63 of the vulvar cancers the hyaline changes dominated the histologic picture (Fig. 5), so that frequently only narrow strands or small agglomerations of lymphocytes remained. These hyaline glands comprised 17 per cent of the total number. Senility could hardly

be held responsible for these changes since they were present in both cervix and vulva cases, in spite of the average age difference in the two groups.

In those cases in which the infected cancerous ulcer had not previously been sterilized by radiation, marked hyperemia of the extirpated lymph glands evidenced either by dilated blood vessels (Fig. 7) or bloody infiltration of the lymphatic tissues, was frequently observed. Such glands were usually large and succulent, often somewhat edematous. Frequently operative wound infection attended their removal.

Without question the most interesting finding in this study outside of the distribution of cancer metastases was the frequency of glands showing endometriosis. As far back as 1898, long before the question of endometrial-like implants in the pelvis had even been thought of, Wertheim found on serial section of lymph glands removed for cervix carcinoma the occurrence of cystlike irregular spaces lined by cylin-

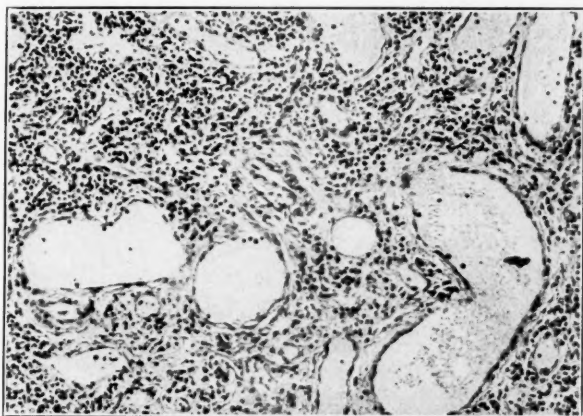


Fig. 7.—Hyperemia of the lymph glands showing marked dilated blood vessels, often found in infected cancers.

dricial epithelium. Since these epithelial structures occurred rather frequently, 48 times in 500 cases (9.6 per cent) of cervix carcinoma and not in a single one of 80 cases free of carcinoma subjected to examination of pelvic lymph glands at autopsy, he concluded that these structures were cancer metastases. Later, when in a second series of 10 autopsies, he found a similar epithelial-like cyst in a patient who died of pelvic infection he retracted his former opinion. Those who opposed Wertheim's views of operative gland removal in cervix cancer brought up a mass of evidence proving that such epithelial proliferations were found in a great variety of conditions not associated with cancer. Schindler in 1906 suggested for the first time a transplantation of uterine epithelium to account for these epithelial inclusions in the tributary lymph glands. The relative frequency of their association with cervix carcinoma was noted by others. Kermauner and Lameris found them in 11 out of 87 cases. Halban and Mestitz in 1926 stressed the endometrial nature of these lymph gland metastases and were in-

clined to interpret other forms of endometriosis of the pelvic organs to lymphatic transport rather than to transtubal implantation according to Sampson. In recent years French writers have again emphasized the occurrence of these epithelial structures in the lymph glands of cervical cancer patients. Michel-Bechet found two endometrial inclusions in 13 cases where glands were removed for cervix cancer. He interpreted them as malignant metastases. Leveuf, Herrenschmidt, and Godard in 36 cases had similar findings and a similar interpretation. Gricouroff on the other hand disproves these conditions of malignancy and found typical endometrial tissue in one out of five cases where glands were removed at autopsy in absolutely normal cases. One recent American contribution to this subject deserves special mention. Hausmann and Schenken in 1933 found two lymph gland endometrioses, one in a 31-year-old woman who had uterine chorioepithelioma and one in a negress dying of nonmalignant causes who had endometriosis of both ovaries as well as in the lymph gland.

In my own series of endometrial implants in the lymph glands, it is significant that none were found in the 381 glands tributary to carcinoma of the vulva. In 90 lymphadenectomy operations for Group II or Group III cervix carcinoma endometriosis was found in 8 cases, three times in two of the glands removed, making a total of eleven glands that showed endometriosis. In addition these structures were found in one hypogastric gland removed at autopsy for cervix carcinoma. There was considerable variation in the microscopic picture in these twelve lymph glands. Sometimes there was a small disc-shaped epithelial inclusion (Fig. 8), sometimes a cystlike structure with irregular contour and epithelial proliferations (Fig. 9), and in two cases the picture resembled closely the morphology of uterine glands (Fig. 10). In all instances the endometrial metastases followed the course of the efferent lymph channels, lying in the large sinuses directly under the capsule of the gland. In none of the 41 out of 90 patients subjected to lymphadenectomy who were over 45 years of age was any endometriosis found. The eight patients operated upon showing endometriosis, all ranged in age from 30 to 42 years. This tends to confirm its relationship with the processes of menstruation. In three patients, both ovaries showed small areas of endometriosis as well as the lymph glands, and in one patient there was in addition to this a double-sided adenomyosis of the uterine portion of the Fallopian tubes. In this last-named patient (Figs. 11 and 12) therefore we found six points of endometrial proliferation, 2 in the ovaries, 2 in the tubes, and 2 in the lymph glands.

By the law of proportion in these 9 cases of lymph gland endometriosis, we should have found cancer metastasis present in one-third of the cases, that is to say in three of them. It so happened, whether by chance or not I cannot say, that in none of the 9 was there such a finding. The coincidence of cancer metastasis and endometrial metastasis has, however, been reported by others. Insufficient data are available at present as to how frequently this occurs.

No one has to my knowledge ventured an explanation of the remarkable frequency of lymph gland endometriosis in cervical cancer, approximately 9 per cent of all cases. This thought occurs to me. The importance of cervical stenosis as predisposing to the retrograde flow of the endometrial particles released at menstruation has been stressed

Fig. 8.

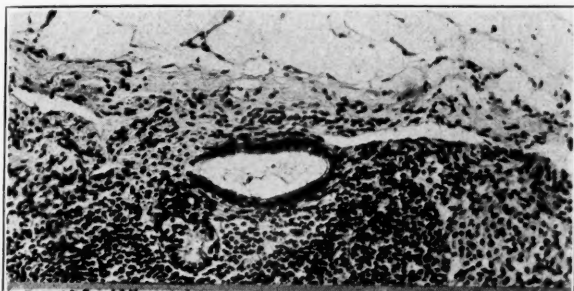


Fig. 9.

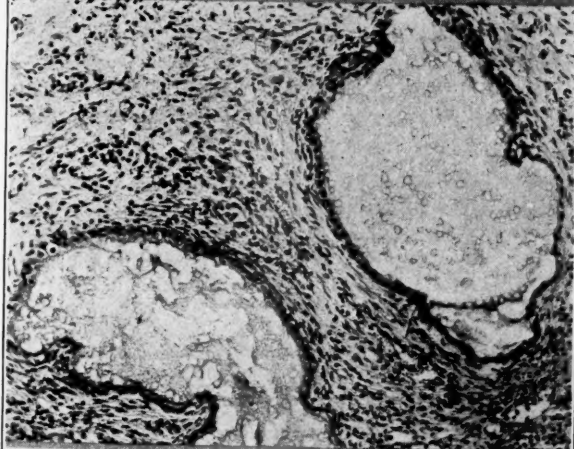


Fig. 10.

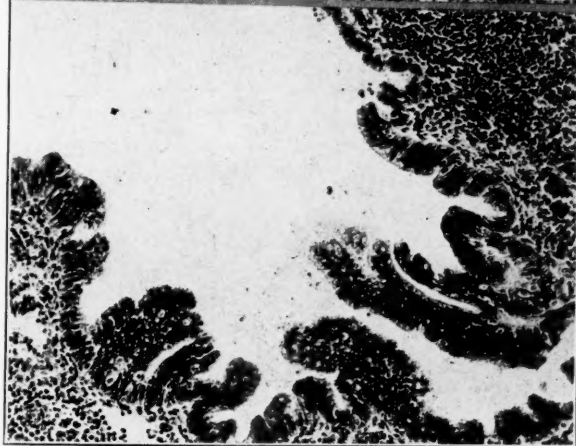


Fig. 8.—Small endometrial implant beneath the capsule of a lymph gland.
Fig. 9.—Epithelium-lined cysts of endometrial origin found in lymph gland.
Fig. 10.—Typical endometrial proliferation in a lymph gland.

by Sampson. May we not assume that a proliferating intracervical carcinoma may similarly block the free exit of menstrual blood and with the lymphatics opened by the ulcer just above the blocking tumor give opportunity for transport of endometrial tissue to the tributary hypogastric and obturator lymph glands. In all of my cases the endometrial metastases were limited to these two groups of lymph glands.

Turning now to the subject of cancer metastases in these lymph glands, we see in Figs. 13 and 14 the anatomic distribution and number found in carcinoma of the vulva and carcinoma of the cervix. The vulvar metastases were found in 30 out of 65 patients operated upon (46 per cent). There were many patients with multiple metastases. The inguinofemoral chain was found involved 40 times, 21 times on the right, 19 times on the left side. In only 5 instances were the deeper glands found involved; on the right side the external iliac twice, the obturator once; on the left side the external iliac and obturator each once. Many

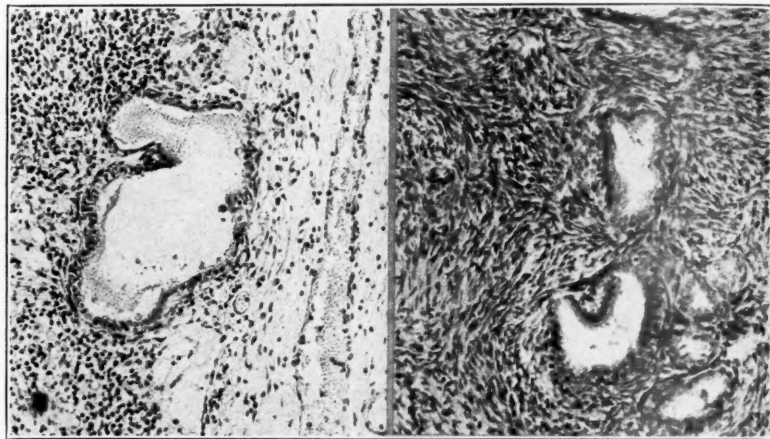


Fig. 11.

Fig. 12.

Fig. 11.—Endometriosis of lymph gland.

Fig. 12.—Ovary from same patient as Fig. 11. In this case two lymph glands, both ovaries, and both tubes showed evidence of endometriosis.

of the larger metastatic glands in the femoral region showed a tendency to central necrosis and those associated with slow-growing well-differentiated cancers were frequently fibrotic. In 10 of the 30 cases with metastases, both sides were involved. In four of the more advanced cases the glands were so firmly adherent to the wall of the femoral vessels that they could not be removed.

In cervix carcinoma metastases were found in 29 out of the 83 Group II lymphadenectomies and in 2 out of the 7 Group III lymphadenectomies. In the latter group technical difficulties made a satisfactory complete operation impossible. We thus have an average of 34 per cent involvement for the entire group and 35 per cent for the Group II series. In 9 patients glands on both sides were involved, and as seen in Fig. 14, the distribution was more varied than in the vulvar cases.

Noteworthy was the rarity of metastases in the external iliac group, noted only in one patient. The left side was far more frequently the site of lymph gland spread, 30 glands compared to only 18 on the right side. The hypogastric glands were affected 33 times out of a total of 48 carcinomatous glands, an average of 68.75 per cent.

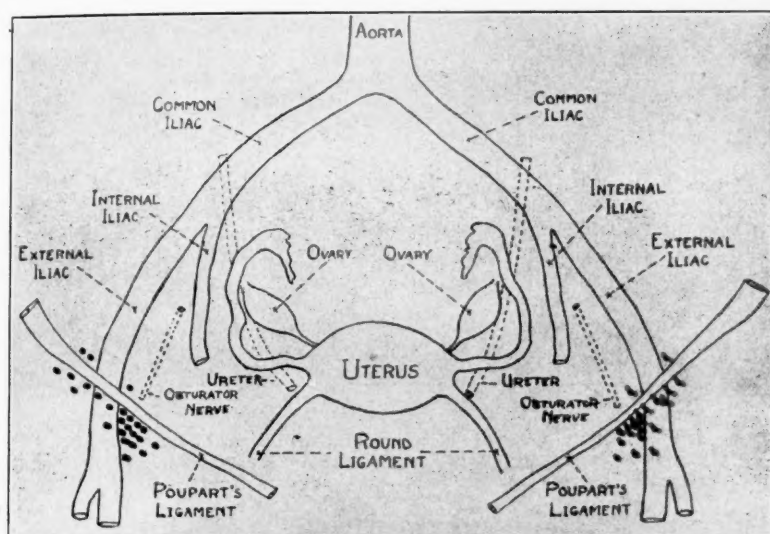


Fig. 13.—Anatomic distribution of cancer metastases in lymph glands associated with vulvar carcinoma: right inguinofemoral lymph chain, 21; left inguinofemoral lymph chain, 19; right external iliac, 2; right obturator, 1; left external iliac, 1; left obturator, 1.

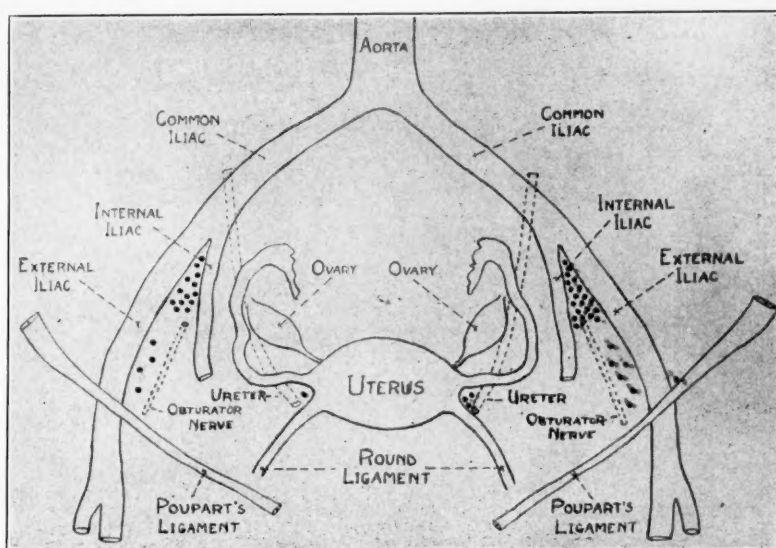


Fig. 14.—Anatomic distribution of cancer metastasis in lymph glands associated with cervix carcinoma: right hypogastric, 13; right obturator, 4; right ureteral, 1; left hypogastric, 20; left obturator, 6; left ureteral, 3; left external iliac, 1.

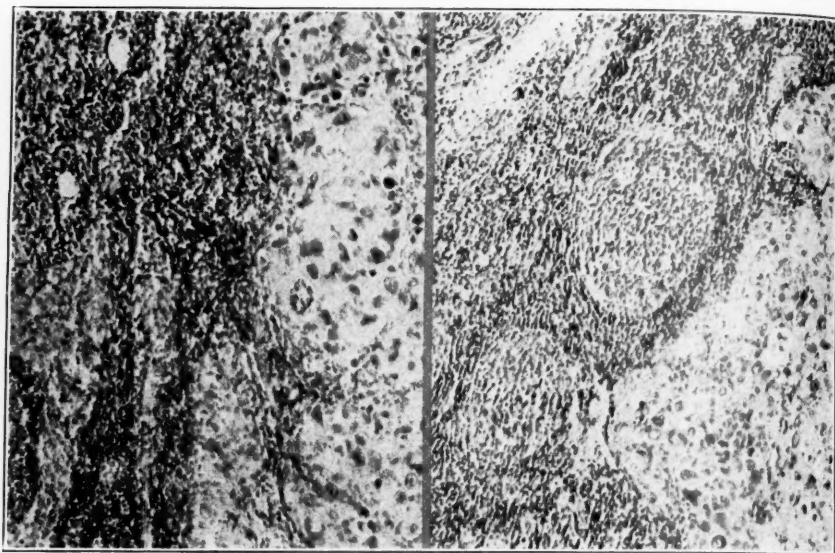


Fig. 15.

Fig. 16.

Fig. 15.—Edge of large subcapsular metastatic carcinoma of lymph gland.

Fig. 16.—Metastatic carcinoma in lymph gland associated with large germinal follicles.

Fig. 18.

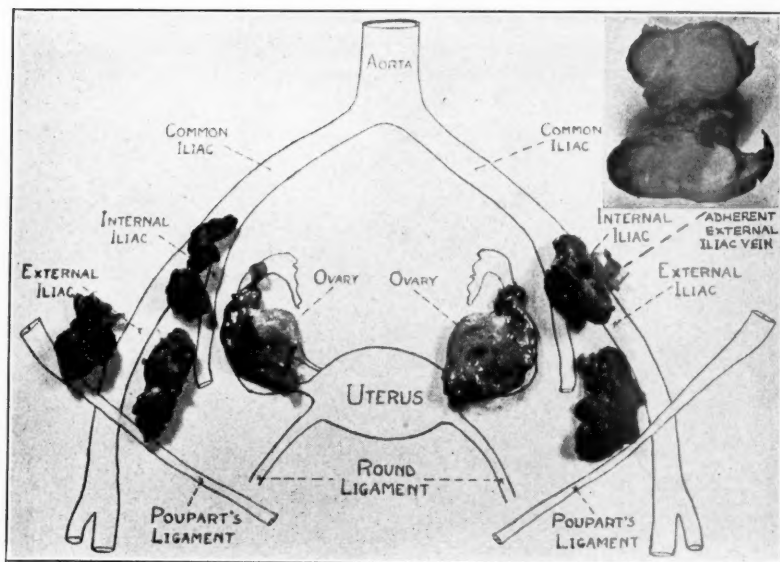


Fig. 17.

Fig. 17.—Anatomic distribution of glands removed in Group II cancer of the cervix. The left hypogastric gland so densely adherent to the external iliac vein as to require resection of this vessel to effect gland removal.

Fig. 18.—Same case as Fig. 17. Cross-section of adherent carcinomatous hypogastric lymph gland.

The size of the metastases varied from a microscopic subcapsular nest in the efferent sinuses to huge masses distending the lymph gland and leaving only a narrow rim of lymphocytes beneath the fibrous capsule (Fig. 15). Out of 36 Group II lymph glands showing carcinoma, it was found that 13 were characterized by follicular hyperplasia (Fig. 16), 2 by endothelial hyperplasia, 11 by hyaline degeneration and fibrosis, and 10 by a diffuse structureless distribution of lymphatic tissue. We can therefore make no deductions as to what type of lymph gland is most frequently the seat of cancer metastases. Wherever the metastatic nodule was small and the structure of the gland well preserved, it was evident that the point of entrance was in the capsular sinuses of the efferent vessels.

A few points as to operative complications and mortality in these lymph gland operations may be mentioned. In the vulvar cases where the Basset double-sided gland removal with vulvectomy was the operation of choice, some degree of postoperative wound necrosis occurred in about 90 per cent of the cases. The average age of 59 years and the debility of many of these patients partly accounts for the poor healing. It also was a factor in the mortality rate, which owing to 2 recent postoperative deaths is now 7.5 per cent, 4 out of 53 complete Basset operations with vulvectomy. The lymphadenectomies in cervix cases, although involving a laparotomy, were done in younger individuals. There were only two deaths in 83 Group II cases, or a primary mortality of 2.4 per cent. The chief complication in this group was operative hemorrhage. In two patients this could only be controlled by clamps and a pack which were later removed without complicating infection. In 4 instances the external iliac vessels (Figs. 17 and 18) were ligated or resected with the adherent glands.

CONCLUSIONS

A total of 1,271 lymph glands removed for carcinoma having its primary seat in the vulva or cervix showed a fairly constant anatomic distribution of the tributary lymph channels.

The five groups studied in this series were the inguinofemoral chain, including Cloquet's gland, the external iliac glands, the obturator glands, the hypogastric glands, and the ureteral glands.

In 864 glands of this series, available for further microscopic study, a great variety of histologic changes were noted. Follicle hyperplasia was relatively frequent in the inguinofemoral chain and in the unirradiated pelvic lymph glands. In the external iliac group fatty infiltration was the usual picture.

There was a striking absence of lymph follicles in those glands that had been subjected to heavy preoperative radiation, so that there is little doubt that follicles are destroyed by this treatment.

The frequency of hyaline degeneration points to a possible connection between this pathologic change and the products of cancer metabolism.

Nine cases of endometriosis in the lymph glands indicate a high incidence of this anomaly with cancer of the cervix. Confirmatory evidence

of the endometrial character of these lesions lies in their association with ovarian endometriosis in three instances. The frequency of lymph gland endometriosis in cervix cancer may possibly be explained by a blocking of the cervical canal with open lymph gland channels above the point of blocking.

Cancer metastases occurred in 46 per cent of vulvar cancers and in 35 per cent of Group II cervix cancers. In vulvar cancer the inguino-femoral chain was most often involved; in cervix cancer it was usually the hypogastric glands.

The operative complications and mortality in these lymph gland operations were relatively slight. Four out of 53 Basset operations ended fatally (7.5 per cent), and only 2 out of 83 patients who had lymphadenectomies for Group II cervix cancer died (2.4 per cent).

REFERENCES

- Gricouroff, G.: Bull. pour l'étude du cancer 25: 759, 1936. Hausmann, G. H., and Schenken, J. R.: AM. J. OBST. & GYNEC. 25: 572, 1933. Kermauner and Lameris: In Halban-Seitz's Handbuch d. Biologie und Pathologie des Weibes 5: 843, 1927. Leveuf, Herrenschmidt, and Godard: L'envahissement des ganglions dans les cancers du col de l'uterus, Assn. franç. pour l'étude de cancer 22: 239, 1933. Leveuf and Godard: Rev. de Chir. 61: 219, 1923. Michel-Bechet: Mém. Acad. de chir. 62: 926, 1936. Mestitz, W.: Arch. f. Gynäk. 130: 667, 1927. Montanini, N.: Tumori 18: 328, 1932. Sampson, J. A.: Trans. Am. Gynec. Soc., p. 228, 1925. Schindler, R.: Monatschr. f. Geburtsh. u. Gynäk. 23: 502, 1906. Sternberg, C.: In Henke-Lubarsch's Handbuch der speciellen pathologischen Anatomie und Histologie 1: 1, 331-340. Welsh, A. M.: M. J. Australia 2: 345, 1934. Wertheim, E.: Zentralbl. f. Gynäk. 27: 105, 1903.

AN EVALUATION OF THE FIVE-YEAR CRITERION IN CARCINOMA OF THE CERVIX*

ROBERT A. KIMBROUGH, M.D., AND PENDLETON TOMPKINS, M.D.,
PHILADELPHIA, PA.

(From the Gynecological Service of the University of Pennsylvania)

THE arbitrary five-year criterion tends to direct interest in the results of radium treatment of carcinoma more toward five-year than toward permanent results. That patients not infrequently die of recurrence of the original growth long after the five-year mark, is a fact well known to all of us. The present study is an attempt to evaluate five-year survival as an index of the permanent cure of cervical carcinoma.

The first approach was to determine the number of patients who survived ten years in proportion to the number of five-year survivors in a group of 304 primary cases of cervical carcinoma treated with radium at the Hospital of the University of Pennsylvania from 1920 through 1927. The series begins with 1920, when Dr. John G. Clark discontinued hysterectomy and adopted radium therapy for all cases of cervical carcinoma. Patients treated since 1927 are excluded so that our ten-year results could be known. Stage V (Schmitz) cases are not included because procedures other than irradiation were employed in their treatment.

Microscopic confirmation of the diagnosis of carcinoma was obtained in all but six of the patients in this series who survived five or more years. It seems unfair to rule out all of the cases in which there was no biopsy, as by so doing 60 advanced fatal cases would also be eliminated and thus falsely raise the percentage of five-year survivors. Follow-up data were obtained in 97.3 per cent of the entire group. The unfollowed cases are included and counted as dead.

TABLE I. FIVE- AND TEN-YEAR RESULTS OF RADIUM TREATMENT OF CARCINOMA OF THE CERVIX (1920-1927)

PATIENTS TREATED	FIVE-YEAR SURVIVORS	TEN-YEAR SURVIVORS
304 (100%)	71 (23.3%)	57 (18.7%)
80 per cent of those who lived five years survived ten or more years after treatment.		

As shown in Table I, 23.3 per cent of the treated patients survived five or more years, and 18.7 per cent of the original group lived more than ten years after treatment. In other words, four-fifths of those who survived five years lived at least ten years after treatment.

In Table II are recorded the five- and ten-year survival rates recently reported by Ward and Sackett from the Woman's Hospital of New York and those of Frank Lynch from the University of California Clinic. Although the latter statistics have not been published, Lynch has kindly given us permission to use them. The striking uniformity of these results confirms William P. Healy's oft repeated statement that

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

TABLE II. COLLECTED FIVE- AND TEN-YEAR RESULTS OF TREATMENT OF CARCINOMA OF THE CERVIX

	DATE OF TREATMENT	PATIENTS TREATED		FIVE-YEAR SURVIVORS		TEN-YEAR SURVIVORS	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Lynch	1916-1927	186	100	41	22.0	34	18.3
Ward and Sackett	1919-1927	344	100	85	24.7	62	18.0
U. of P. Series	1920-1927	304	100	71	23.3	57	18.7
Totals		834	100	197	23.6	153	18.3

regardless of methods of treatment the five-year survival rate is near 20 per cent. Study of the composite group made up of Ward's, Lynch's, and our cases shows that of 197 patients who survived five years, 77.6 per cent lived ten or more years after treatment.

The second approach to our evaluation of the five-year criterion is concerned with an entirely different group of cases. Of all the patients treated for cervical carcinoma in our clinic from 1913 through 1927 87 with microscopic proof of cancer have survived five or more years. Every patient in this group has been traced to the present time.

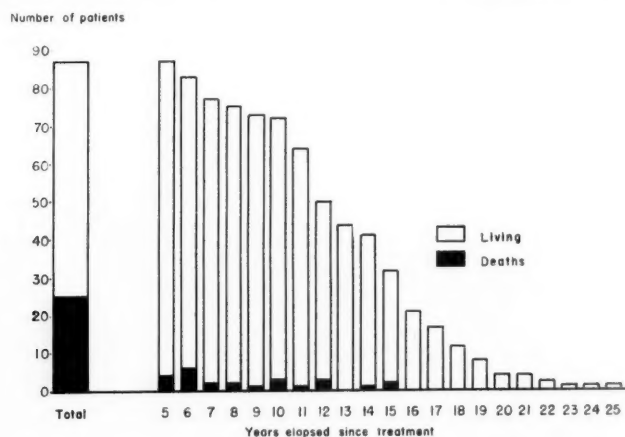


Chart 1.—Mortality subsequent to five-year survival of 87 patients treated, 1913 to 1927.

Chart 1 shows the follow-up data on 87 patients who survived from five to twenty-five years after treatment. The first column shows the total mortality and the following columns depict the time of death subsequent to five-year survival. The total mortality in this group is 29 per cent. Most of the deaths occurred in the second five-year period following treatment. The explanation of this will be found in Chart 2.

Chart 2 presents the causes of death under three categories, (1) from extension or recurrence, (2) from unknown causes, and (3) from causes other than cancer. Sixteen patients (18.4 per cent) are known to have died of cancer. It will be noted that most of these deaths occurred in the second five-year period after treatment. Four other patients have died of unascertained causes; if these four deaths be considered due to cancer, the total cancer deaths in the group are 20 (23.0 per cent). After surviving 12 or more years 5 patients died from causes not related to the

original cervical malignancy, viz., (1) Ludwig's angina (autopsy), (2) cirrhosis of the liver (autopsy), (3) cardiorenal disease at 68 years of age, (4) "old age" at 75 years, (5) pneumonia at 44 years.

Although 44 of our patients survived more than thirteen years, no death attributable to cancer has occurred longer than twelve years after treatment.

Chart 3 depicts in another form the follow-up data on the groups of patients who survived five and ten years, respectively.

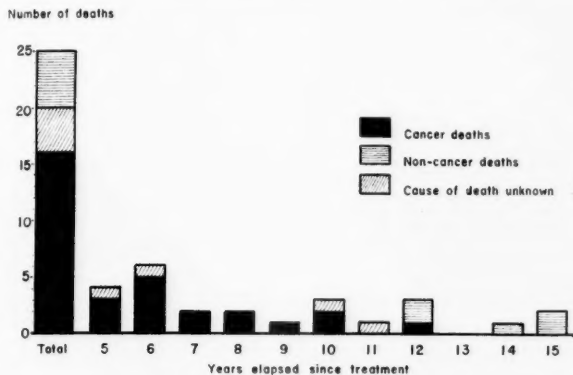


Chart 2.—Causes of mortality of 25 patients subsequent to five-year survival.

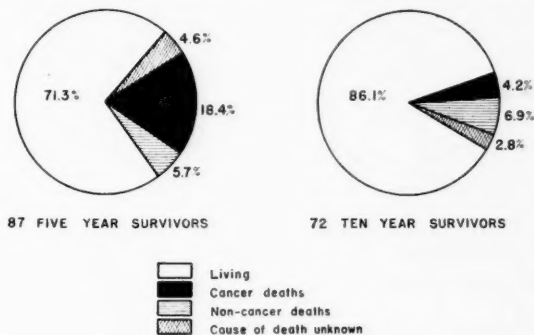


Chart 3.—Present status of five- and ten-year survivors.

SUMMARY

Seventy-eight per cent of 197 patients who survived five years lived 10 or more years after treatment.

Of 87 patients who survived five years after treatment, approximately 20 per cent subsequently died of cancer.

Seventy-two patients survived more than ten years and only 4 per cent of these died of cancer.

Forty-four patients lived thirteen years or more after treatment and none of these has died of cancer.

The complete follow-up records which made this study possible are due in large measure to the untiring efforts of Miss Etta Jones, to whom we acknowledge our indebtedness.

DISCUSSION OF PAPERS BY TAUSSIG, AND KIMBROUGH AND TOMPKINS

DR. BROOKE M. ANSPACH, PHILADELPHIA, PA.—Dr. Kimbrough's paper brings out the fact that while five years as an arbitrary period does not indicate the final salvage of patients with carcinoma, it is a very reliable index of the way things are going. His statistics indicate that 71.2 of the five-year salvage and 86 per cent of the ten-year salvage is likely to be maintained.

There must be considerable difference in our attitude toward cancer of the cervix and cancer of the vulva. Vulvectomy followed by a bilateral extirpation of the glands may be likened to that for breast cancer where with the breast and the pectoral muscles the surgeon removes all of the lymph tissue in the axilla. Both of these procedures bear relatively little risk. In both instances the areas are more easily accessible and the mortality is low. It is a different matter with cancer of the cervix, for here there is much more difficulty in the removal of the diseased glands.

Adenectomy supplementing treatment with radium involves certainly less risk when it is confined to the removal of the carcinomatous glands. But a complete pelvic adenectomy must carry with it a higher primary mortality than adenectomy in carcinoma of the vulva.

Dr. Taussig's studies may be interpreted as giving an additional reason for depending to a great extent upon radiation in the treatment of cancer of the cervix, for he found that the larger the dose of radon units the greater the effect upon the lymph follicles in the pelvis. If the lymph nodes are affected, the cancer nests in them are exposed to the same influence and the types of cancer cells amenable to radiation are favorably influenced. This does not mean that radiation destroys the cancer nests uniformly, since they were present in 34 of Dr. Taussig's lymph-adenectomies.

His findings relative to endometriosis suggest the probability that the lymph glands of the pelvis are not uncommonly the seat of this disease, and if they are it would lend color to the theory of the direct growth or deportation of the endometrial tissue, either through the lymphatic spaces or the tubes, rather than an explanation of endometriosis on the grounds of an early metaplasia of the cells that originally line the peritoneal cavity.

DR. CHARLES A. BEHNEY, PHILADELPHIA, PA.—Three reports (Ward and Sackett, Lynch, Kimbrough) have independently shown the ratio of the ten-year to the five-year salvage in carcinoma of the cervix treated with radium. The grand total of the three series becomes numerically important. One can now safely expect a ten-year salvage of 75 per cent of the patients who have survived five years. It is interesting in this connection to note that Shaw, reporting a series of 154 patients with carcinoma of the cervix treated by the Wertheim operation, found that 72 per cent of those who survived the five-year period were living and well ten years after operation.

Though less reprehensible it is just as incorrect to depreciate cures as to exaggerate them. It has always seemed unfair to attribute all deaths in patients who have had carcinoma to the disease. If other studies of the cause of death after five years' survival confirm Dr. Kimbrough's findings, a basis for more accurately estimating end results will be available.

It has been stated that high voltage x-ray therapy will not destroy carcinoma cells in the lymph nodes of the pelvis. Those of us who have seen carcinoma in the cervix, the fundus, the ovaries, and throughout the peritoneal cavity melt away after deep x-ray therapy doubt that the discovery of cancer cells in lymph nodes after irradiation proves that in these nodes carcinoma is *never* destroyed by this therapy. Dr. Taussig's observation that the lymph follicles decreased as the irradiation dosage was increased indicates that there is a marked irradiation effect on these nodes. I should like to inquire whether he has a record of the comparative lymph node metastases found with the different irradiation dosages.

In reviewing our records at Philadelphia General Hospital we find that 63 patients with microscopically proved carcinoma of the vulva have been admitted since 1922. Of these only five are still alive. These depressing results are doubtless due in part to our lack of Dr. Taussig's skill, and in part to the fact that in all of our patients the disease was well advanced. Twenty-six per cent of them lived less than one month after admission and 60 per cent were dead before six months had elapsed.

Of the 58 patients who died on our service, the neoplasm originated on the clitoris in 15, and on other portions of the vulva in 43. As a group, those with carcinoma of the clitoris were younger than those whose growth originated in other portions of the vulva. Squamous cell carcinoma was the predominant type and the majority of tumors were of the more radioresistant grades. There was one patient with sarcoma of the clitoris.

Thirteen of our patients were examined post mortem. In 4 of these, metastases, proved histologically, occurred in more distant situations than the inguinal nodes, the vagina, the rectum, or the bladder. The metastatic sites were as follows: lungs, pleura, liver, spleen, adrenals, kidneys, and nodules in the skin of the thigh. The occurrence of distant metastases, 31 per cent, in our series of vulvar carcinoma is strikingly like that found in our series of carcinoma of the cervix, 33 per cent.

Dr. Taussig's observations and the results he has secured indicate that extensive vulvectomy, with excision of all the regional nodes, and high voltage x-ray irradiation is the best treatment for patients in whom the disease is not too far advanced. For those in the latter stages of the disease, good palliative results can be secured, fairly consistently, with high voltage x-ray therapy.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—In a group of 101 patients treated with radiation from 1921 to 1928 on the Gynecologic Ward Service, Jefferson Medical College Hospital, we obtained a five-year salvage of 28 patients, or 27.7 per cent. Of these, 19 patients, or 18.8 per cent, were alive at the end of the ten-year period. This shows that 67 per cent of the 28 patients living for five years were salvaged for ten or more years. If we include 2 patients who died in the tenth year, but not of cancer, it would raise the ten-year survival rate of patients salvaged for five years to 75 per cent, corresponding approximately to Dr. Kimbrough's findings.

PROFESSOR LUDWIG ADLER, formerly of VIENNA.—Although I cannot give you exact figures since I was unable to bring my notes and papers from Vienna, I think that I may have a slightly higher percentage of cancer patients living after ten and fifteen years than Dr. Kimbrough's figures show. His investigations are important since it has been suggested that one should not take the five-year cures but only the ten-year cures as permanent. As the time following treatment increases, our patients become older and therefore, of course, their life expectancy decreases, with the result that more die from other causes. According to strict statistics deaths of all patients are considered as recurrences unless it is proved by post-mortem that the patient was free from a recurrence. Furthermore, the greatest part, about 80 per cent, I think in my cases it may be between 80 per cent and 90 per cent, of the women cured after five years are still living and free from cancer after ten years. For these reasons, therefore, I think the ten-year or the fifteen-year standard should not yet be adopted.

I would like to ask Dr. Taussig whether he has also made the observation that the involvement of the glands in cervical cancer does not always follow the anatomical route? One finds the glands in the pelvis uninvolved sometimes and yet in the same individual glands higher up will be found to be cancerous.

In this connection I should like to draw your attention to the fact that when the removed glands were carcinomatous, the patient was very rarely found to be free from recurrence after five years. Schauta's statistics proved this statement. This is one reason why the pupils of Schauta have stuck to the vaginal operation instead of adopting Wertheim's laparotomy.

In a series of more than 800 cases of the radical vaginal operation our mortality rate was only about 3.9 per cent in comparison with the mortality of laparotomy, which, according to the statistics of the best men like Wertheim and Bonney, is as high as 15 per cent; in others even higher. For this reason we have felt that we should stick to the vaginal operation; all the more so because radiation treatment might take care of the glands. However, I begin to doubt whether this belief is correct after hearing what Dr. Taussig has said regarding the effect of radiation on carcinomatous glands.

Since the year 1916 I have systematically combined operation with radiation. I introduce radium immediately after the closing of the peritoneum in the radical vaginal operation, and radiate later with x-ray and radium. My results, which were first published at the International Congress in Stockholm, 1928, showed nearly 31 per cent of absolute cures resulting from the vaginal operation. Since then, I believe, my results have been even better.

I do not think that radiation on the one hand and operation on the other hand will be the final solution of the problem of cancer treatment. Since 1920 I have always advocated the so-called elective treatment, that is, I think that the method of treatment should be adapted to the general and local conditions in each case. I do operate on all operable cases if there is no contraindication against operation. My routine procedure is the radical vaginal operation; laparotomy is used exceptionally. In every case I introduce radium during the operation and use prophylactic radiation with radium and x-ray later. In all inoperable cases radiation is used and also in some operable cases, especially in the so-called borderline cases and when the condition of the patient is not good. With this selective treatment I have obtained between 38 per cent and 39 per cent absolute cures.

DR. CURTIS F. BURNAM, BALTIMORE, MD.—In general, the ten- or fifteen-year, and twenty-year cure rates, reported by Dr. Kimbrough, coincide with our own observations, which I reported in 1931. I recently saw a woman who had been treated in 1911 for cancer of the cervix by radiation, and who is still well. We have two other cases from that year.

My impression is that late recurrences are most likely to occur in those cases which originally were extensive, inoperable or borderline. The early cancers treated, that remain well for five years, usually stay well. It is, therefore, of interest in such reports as Dr. Kimbrough's to state the extent of the disease at the time of the original treatment.

Dr. Taussig, apparently, limits a removal of the pelvic lymph glands to cases in Groups 2 and 3. Undoubtedly, there is a greater incidence of lymph gland metastases in these advanced cases than in Group 1. Nevertheless, many of these do have metastases. The percentage of cures of early cases for different years, has varied from 100 per cent to 25 per cent, and this variation has been due almost exclusively to glandular metastases.

I must take exception to Dr. Taussig's statement that carcinoma involving the lymph glands of the pelvis cannot be eradicated by x-ray. I am quite sure that it can be in a considerable number of cases. It should be borne in mind, however, that there is a vast difference in ray sensitivity between different cases. I do not think this is due to the differences in histologic grading, but principally to differences in individual resistance of the patients concerned. So far as I know, we have never seen a case cured where there has been definite involvement of the glands above the pelvis in the retroperitoneal lumbar region.

A dosage of 5,000 r. units to the glands themselves, which Dr. Taussig says is the amount used in his cases, is a considerable one, and to give it safely, one should take from three to six weeks or even longer. My associates and myself, on the average, have used less milligram hours than most of the groups in this country and abroad. Nevertheless, in recent years, since we have begun using x-ray in conjunction with the radium, our tendency has been further to reduce the radium dosage.

DR. KIMBROUGH, Jr. (closing).—For statistical reports I am still in favor of the five-year criterion but in using it we must bear in mind that subsequent to five-year survival approximately 20 per cent of patients will probably die of cancer.

DR. TAUSSIG (closing).—So far as cervix cancer is concerned there is no doubt that Group II cases are greatly benefited by the gland removal operation. I have now performed 86 such operations and have had but two deaths. That means that it is a safe operation so far as my individual experience is concerned. The mortality is much higher in the Bassett lymph gland removals for cancer of the vulva. It is easy to remove the pelvic glands in this way, and I am convinced that, while we are eliminating only two-thirds of the possibly carcinomatous glands of the pelvis, we have made a definite step in advance.

We have all seen the failure of heavy x-radiation to influence lymph gland metastasis. It is the experience of most x-ray men, that regression by this method is temporary, and that surgical removal of the glands is necessary for permanent cure.

On the question of endometriosis in lymph glands, it should be remembered that Wertheim, when he first began to perform his operation for cancer of the cervix, found in 48 out of 500 operations peculiar epithelial structures in the lymph glands. He thought they were carcinomatous at first but later finding them in noncancerous patients gave up the idea of classifying them as such. Recent work has shown that these are definitely of endometrial origin. I would like to suggest the following explanation of the marked frequency of lymph gland endometriosis in cervix cancer. It occurs in 9 per cent of such cases according to Wertheim's figures, and in my own series there was approximately the same percentage. In recent reports of French operators there has been a similar high incidence of lymph gland endometriosis. My theory is that since the cervix is partly or completely blocked by the carcinoma, the endometrial particles at menstruation cannot gain an exit through the cervical canal. Above the point of carcinoma blockade there are open lymph channels and through these the particles of endometrium are readily carried out through the lymphatics to the tributary glands.

MASCULINIZING TUMORS OF THE OVARY
(ARRHENOBLASTOMA, ADRENAL OVARIAN TUMORS)*

WITH REPORT OF 6 ADDITIONAL CASES OF ARRHENOBLASTOMA

EMIL NOVAK, M.D., BALTIMORE, MD.

(From the Department of Gynecology, Johns Hopkins Medical School)

NOTWITHSTANDING their relative rarity, no group of ovarian neoplasms has excited more interest in recent years than those which have been shown to produce striking biologic effects upon the sex characters of the individual. That tumors of the ductless glands may bring about remarkable endocrinopathies had been known long before we began to speak of masculinizing or feminizing tumors of the ovary. Perhaps the first demonstration of this, on the basis of histologic and clinical rather than hormonal studies, was in the case of the pituitary. Although the growth hormone of the hypophysis has not yet been isolated, it has long been accepted, and on good scientific grounds, that overproduction of this hormone by adenomas involving the eosinophilic cells, the normal producers of the growth hormone, is the responsible factor in acromegaly and gigantism.

Since then an imposing group of syndromes has been shown to be due to tumors of one or other of the endocrine glands. Among such tumors the following may be mentioned as producing clinical syndromes which are rather clearly defined, viz., eosinophilic adenoma (already mentioned), basophilic adenoma and chromophobic adenoma of the pituitary, adenoma of the parathyroid, adenoma involving the islands of Langerhans in the pancreas, adenoma or carcinoma of the adrenal cortex, tumors of the adrenal medulla, and certain tumors of the gonads, male and female.

By contrast with the feminizing tumors which constitute the granulosa cell carcinoma group, the masculinizing variety, the arrhenoblastomas, are quite rare. The former make up approximately 10 per cent of all primary carcinomas of the ovary, and we have encountered, in our own material, and in that sent in from other clinics, no less than 68 instances. On the other hand, I have been able to collect from the entire literature only 45 cases of arrhenoblastoma, to which must be added the 6 cases included in the present report. In 1933 Sedlacek¹ was able to collect only 27, and in 1934 Kleine² added 8 more, including 4 of his own. Since then, additional cases have been reported by von Szathmary,³ Phelan,⁴ Gnassi,⁵ McLester,⁶ Baldwin and Gafford,⁷ Young and Te Linde,⁸ Schiller⁹ (also reported by Föderl), Schockaert,¹⁰ Miller¹¹ and Norris.¹² The case reported by Behrend and Levine¹³ in

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

NOTE: For lack of space, parts of this article and Figs. 2, 3, 4, 7, and 17 have been omitted but the complete paper may be had in the author's reprints.

1936 I am omitting, as both the clinical and pathologic descriptions, as well as the photomicrograph of its histologic appearance, make it seem extremely doubtful.

* * *

Gross Pathology.—These tumors, as encountered at operation, are usually of moderate size, and may be very small, though in a number of reported instances they have reached large proportions, even to the size of a man's head. Characteristically, especially when of small size, they are solid tumors, though they not infrequently exhibit one or more cystic areas, and in the larger tumors the cysts may be of large size. The color and consistency are variable, depending upon their widely differing histologic structure. They may be grayish, with frequently areas of definitely yellowish hue, but in some, the color of the cut surface is bluish, purplish, or reddish-blue. The consistency may be quite firm in some cases, but degenerative changes are common, as is hemorrhage. In some reported instances, especially those of the testicular adenoma type, the tumors have been described as of elastic feel, like normal testicular tissue.

Microscopic Examination.—A description of the microscopic characteristics of arrhenoblastoma is not easy, because of the extreme variations which may be encountered in different cases, and in different parts of the same tumor. At one extreme is the highly differentiated variety corresponding to the testicular adenoma described by Pick in 1905, and characterized by a very definite tubular structure, reproducing more or less perfectly the structure of normal testicular tubules. At the other extreme is the very undifferentiated variety which at first sight may be considered a typical sarcoma, and in which only very careful study of many blocks may reveal the presence of sex-cordlike structures, or imperfect tubules, or lipid-containing cells corresponding to interstitial cells. Finally, in the group designated by Meyer as the intermediate, one finds usually a varying number and distribution of definite tubular structures, interstitial cells, and of cell columns arranged in rather zigzag fashion, quite like the sex cords seen in the early development of the gonads.

* * *

Malignancy.—While arrhenoblastoma is properly classified as a malignant tumor, there is no doubt that its degree of malignancy, like that of granulosa cell carcinoma, is much less than that of ovarian cancer in general. On the other hand, it must be remembered that many of the reports of this newly-recognized and interesting tumor type have been made very soon after their observation, so that one cannot always be certain whether or not later recurrence had occurred. Even so, there are already available sufficient reports to indicate that in some cases the tumor may exhibit highly malignant characteristics. The case previously reported from this laboratory (Novak and Long) terminated fatally, as did also 2 cases reported by Meyer. Moreover, recurrence of the tumor occurred in the case reported by Taylor, Wolfermann and Krock, that of Kleinhaus, and also in the recent case of von Szathmary.

On the other hand, in the great majority of cases reported in the literature, the patient has remained well after removal of the ovary, in spite of the fact that the operation performed was most frequently of conservative nature, usually unilateral salpingo-oophorectomy. It is too soon as yet to offer any worthwhile figures as to the frequency of recurrence and the degree of malignancy, but on the basis of the literature to date there is ample justification for the statement that the degree of malignancy of these tumors as a class is far lower than that of ovarian cancer in general. The same statement can be made concerning granulosa cell cancer and dysgerminoma.

Clinical Features.—Arrhenoblastoma of the ovary occurs most frequently in relatively young patients, the decade between 20 and 30 showing the largest incidence. The youngest patient, so far as I can find, was 15. It is relatively rare beyond the menopause, though rather surprisingly, all 4 of the group recently reported by Kleine² were beyond 50, and Meyer has described such a tumor in a patient of 66.

The clinical course of these patients is characteristically divisible into two phases. There is first a stage of defeminization in which certain typical feminine characteristics are subtracted from the patient, and this is followed, with possible overlapping, by a stage of masculinization, in which certain positive masculine characteristics are added. Chief among the defeminization symptoms are amenorrhea, atrophy of the breasts, and loss of the subcutaneous fatty de-



Fig. 1.—Extreme facial hirsutism in a case of female pseudohermaphroditism due to adrenal cortical hyperplasia, as was later demonstrated by autopsy.

posits which are responsible for the rounding of the feminine figure. Of the masculinization signs, the chief are hypertrophy of the clitoris, hirsutism, and deepening of the voice.

The first symptom noted by most patients is amenorrhea, which may come on abruptly. Regression of the mammary glands soon occurs. Changes in body contour may not be conspicuous and are often not noticed by the patient herself or at least not until hirsutism has developed. The aberrant growth of hair, in my experience, does not usually reach the degree observed with adrenal cortical lesions. For example, Fig. 1 shows the very heavy facial growth of hair in a patient with bilateral cortical hyperplasia, as proved by operation, though no lesion of the ovary was present. In arrhenoblastoma patients the facial hirsutism may be sufficiently heavy to compel daily shaving. In addition there may be extensive hirsutism of both the upper and lower extremities, with perhaps also much hair on the

abdomen and chest. In some cases, on the other hand, the hirsutism may be very moderate, and the pubic hair may retain its characteristically feminine horizontal upper border, as in my Case 1.

At this point I may again emphasize that hirsutism in itself is not necessarily an evidence of masculinization. There are many otherwise typically feminine patients, who menstruate normally, and bear many children, and whose physical and psychologic characters are otherwise perfectly feminine, who nevertheless show extensive hirsutism, as every gynecologist knows. While the adrenal is undoubtedly concerned with both hair distribution and sex characteristics, there is no evidence that the two functions are combined in the same cells or group of cells. As a matter of fact, there is reason to believe that the frequent association of hirsutism with more characteristic masculinization phenomena may be incidental, as a result of associated involvement of two separate cell types or groups.

The loss of the typically rounded female contour may be pronounced or it may be only slightly marked, and the duration of the tumor as well as the degree of its secretory activity, would seem to explain these individual variations. Loss of body weight is a common observation, as would be expected from the decrease of subcutaneous adipose tissue.

The changes in the patient's voice are often very noticeable, she herself often attributing this to a persistent "cold" or laryngitis, as in my Case 1. A normally soft, high-pitched feminine voice may be changed to a baritone or even to a basso, with often hoarseness or roughening of the voice. These vocal changes are due to lengthening of the vocal cords, while in marked cases there is overgrowth of the laryngeal cartilages, with the development of a prominent "Adam's Apple."

With reference to the hypertrophy of the clitoris, here again there are marked individual variations. In some cases it is only slight, in others the clitoris may assume the proportions of a miniature penis.

* * *

Effects of Tumor Removal on Symptoms.—The crucial clinical test in the substantiation of a diagnosis of arrhenoblastoma is the regression of the abnormal masculinization symptoms after the removal of the tumor. Though this regression may not be complete in every case, it is usually striking in undoubted cases of arrhenoblastoma. The return of menstruation is the first manifestation of returning femininity, and in general the symptoms disappear in an order the reverse of that of their appearance. Almost without exception menstruation has reappeared about twenty-eight days after the removal of the tumor. One of the few exceptions is my Case 1, though here the failure of the period to occur at the end of the first postoperative month is readily explained by the fact that the patient was extremely ill at that time as a result of a pelvic abscess, with a temperature of

about 104.5° F. for a number of days. The following month, however, the period occurred, and has been entirely normal in character and rhythm since that time.

Another rather prompt evidence of refeminization is the development of the breasts, so that within a few months they are often quite normal. The same thing applies to the general body weight and the body contour.

When we come to the positive manifestations of masculinization, however, we find that these disappear much more slowly than those of defeminization, and often incompletely. When hypertrophy of the clitoris is very marked, the organ may remain abnormally large, so that amputation may be called for. In the milder cases, however, regression is definite though sometimes rather slow. The disappearance of the abnormal hair growth is often a rather slow process, requiring many months, though in many reported cases, as in my Case 1, the recession has been much more rapid.

In a number of the reported cases, pregnancy has been observed to occur after removal of the tumor. One of my patients (Case 2) has had two pregnancies in the two years since operation, though she miscarried each time. Another (Case 4) gave birth to a living full-term child fourteen months after operation. Sedlaczek, in the 27 cases collected by him, found that 5 patients had become pregnant, 2 within two years following operation.

CASE REPORTS OF ARRHENOBLASTOMA

CASE 1.—This patient, aged 35, was referred to me on October 20, 1937, by Dr. J. G. Howell, of Catonsville, Md. She had been quite normal until November of 1936, when menstruation, which had previously recurred at regular four-weekly intervals, had ceased abruptly. There had been one full-term pregnancy seven years previously. During the past ten or eleven months she had developed a considerable growth of rather long downy hair on the upper lip, cheeks, and chin. The legs and arms had been somewhat hairy since puberty, but the hair growth on the extremities had recently become much heavier. The breasts had become much smaller and flatter, and since June the patient had been suffering, as she said, with a persistent "laryngitis" which made her voice rough and much deeper than formerly. She had herself noticed an enlargement of the clitoris. Recently there had been occasional aching pain in the right lower abdomen. There had been no impairment of libido.

The examination showed the weight of the patient to be 119 pounds, and her height 5 feet, 5 inches. The contour of the figure was rather angular, and the breasts were very flat (Fig. 2). The hairy growth was as above described, with also a heavy growth covering the lower abdomen and with a distinctly masculine crines.

Pelvic examination showed moderate but definite hypertrophy of the clitoris, which measured 4½ cm. in length, with a much thickened body, and a glans something over 1 cm. in diameter. The uterus was rather small and pushed slightly to the left by an ovoid, freely movable mass of rather elastic feel, about the size of a lemon, evidently a small tumor of the right ovary. The left adnexa were normal. In view of the history and the pelvic findings, a presumptive diagnosis of arrhenoblastoma was made.

Operation, on Oct. 27, 1937, revealed the tumor of the right ovary to be about the expected size, with smooth external surface, and of elastic feel, so that externally it resembled a cyst, though when it was later cut into, it proved to be an entirely solid growth, as will be described below. The left ovary was below the average size, with a whitish, opaque, and rather corrugated surface, and with no

external evidence of follicular activity. A right salpingo-oophorectomy was done and the appendix was removed. Both adrenal glands were carefully palpated, showing no appreciable enlargement and no palpable nodules.

The convalescence of the patient was marred by the development of a late pelvic abscess, presumably due to infection of a hematocele, and she ran a febrile course for many days before the abscess was evacuated by pelvic puncture on November 8. During this period the patient was quite weak and prostrated, though the later recovery was uneventful.

Postoperative Course.—Probably because of the patient's poor condition for some weeks after operation, the first menstrual period did not occur until January 18, just about twelve weeks after operation, but since then it has recurred regularly at intervals of about four weeks, the duration being four or five days, and the amount moderately free. The breasts have returned to their original size, the facial hair has practically entirely disappeared, and the hair on the extremities has become much less in amount. Especially striking has been the change in voice, which now again is high-pitched instead of having a rough baritone quality. The clitoris is

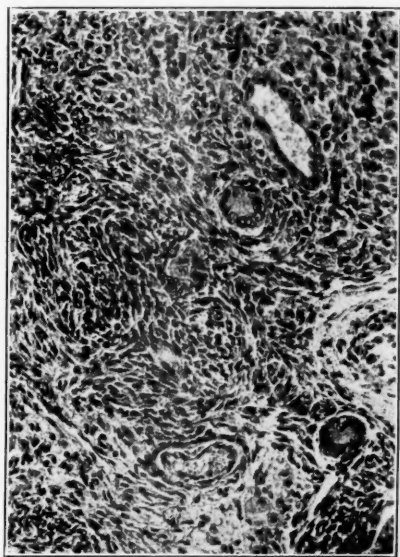


Fig. 5.—Another area in Case 1, showing definite tubules, with a picture quite characteristic of the intermediate type of arrhenoblastoma. This is the prevailing pattern in Case 1.

still above average size, though noticeably smaller than before operation. A pelvic examination made very recently, seven months after operation, shows no indication of recurrence.

Report of Pathologic Examination.—The specimen was a globular mass, measuring 5.5 cm. in diameter, with a normal tube appended. The external surface was quite smooth, and on section the tumor proper was seen to be surrounded by a thin cortical layer of what looked like normal ovarian tissue. The tumor itself presented in most places a reddish-purple, hemorrhagic appearance, with other areas which were grayish and granular, and with a yellowish tinge here and there.

The microscopic examination, like the gross, showed the tumor to be obviously of medullary origin, the cortex being flattened out about the tumor, and showing a few Graafian follicles in various stages of maturation, together with a rather large corpus albicans. Beneath the cortical layer the tumor itself presented a rather sharp though slightly lobulated outline. Its central margin extended well toward the hilum, where thin strands of cells, resembling sex cords, passed into the region of the rete ovarii. In this deeper portion the tumor itself showed some tubular struc-

tures closely resembling the rete tubules of the normal ovary (Fig. 3). Sections from all parts of the tumor showed all stages of transition from sarcomalike areas, to areas in which there was a definitely cordlike arrangement of the cells, to still others with occasional well-defined tubules, and finally areas with a very conspicuously tubular pattern. The cells in the compact areas were round or spindle-shaped, with deep-staining nuclei of various shapes and sizes. The lining epithelium of the tubules varied somewhat, though for the most part it was either cuboidal or columnar, with ovoid, granular nuclei. A few mitotic figures were seen. In some sections one found columns or alveoli of large, eosin-staining polyhedral cells, which morphologically resembled the interstitial cells of the testis, and this impression was given support by the fact that abundant lipoid was demonstrable in these cells by differential staining.

CASE 2.—H. D., a young woman of 24 years, had been quite normal until twenty months before I first saw her, on Aug. 19, 1935, through the kindness of Dr. W. C. Caudill, of Pearisburg, Va. She had been married six years, and had had one nor-

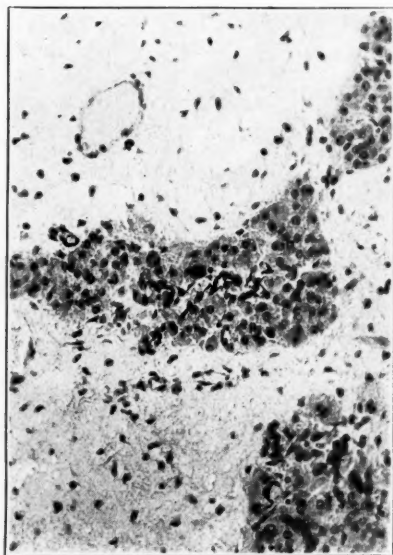


Fig. 6.

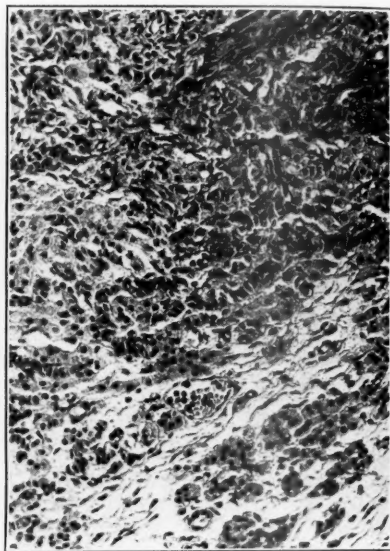


Fig. 8.

Fig. 6.—Aggregations of cells which morphologically, and in their lipoidal staining, exactly resemble the interstitial cells of Leydig of the normal testis.

Fig. 8.—Microscopic appearance of tumor in Case 2. Note the characteristic cords of cells, with nuclei perpendicular to the long axis of the cords, and also the islands of interstitial cells to the left.

mal childbirth five years previously. There had been complete amenorrhea for two years before I saw her, though there had been a rather profuse whitish leucorrhea. About a year ago a growth of hair appeared on her face, involving the upper lip, chin, and both cheeks, with also a heavy hair growth on the upper and lower extremities and on the abdomen. The breasts had become small and flaccid, and the voice had become markedly deeper.

The patient, on examination, was 5 feet, 4 inches tall, and weighed 134 pounds. The general build was normal, though there was a tendency to angularity. There was a moderately heavy growth of dark hair on the upper lip and cheek, with much less on the chin, and a heavy growth on both upper and lower extremities. The pubic hair was of the masculine type, extending in the midline to the umbilicus. There was no enlargement of the thyroid, and both breasts were small and flaccid, with no secretion.

The pelvic examination disclosed a marital outlet, without relaxation. The vaginal mucosa was reddened and congested, with slight leucorrheal discharge. The cervix was only slightly lacerated, and pointed downward and forward. The uterus was small, moderately retroflexed and freely movable. In the left side of the pelvis could be felt an ovoid, freely movable mass about the size of a lemon. It was of rather elastic feel, and was obviously a neoplasm of the left ovary. The right adnexa seemed normal.

A presumptive diagnosis of arrhenoblastoma was made, but as circumstances made it impossible for the patient to remain in Baltimore, she returned to her home and was operated upon shortly afterward (September 3) by Dr. Albert H. Hoge, of Bluefield, West Virginia, who was good enough to send me the tumor which was removed.

Report of Pathologic Examination.—The specimen consisted of a tumor measuring 9 by 8 by 6 cm. The surface was smooth and of bluish white color. Attached to one side was a normal Fallopian tube. The cut section of the tumor showed it to contain many small cystic cavities, some containing a clear fluid, others a mucoid material, while other areas were solid, and of puttylike appearance and consistency.

Microscopically this tumor, like that in Case 1, was apparently of medullary origin, well-circumscribed, and moderately lobulated. It was of interest, however, that in this as in other tumors of this type which I have examined, arrhenoblastomatous elements occurred outside the tumor proper, which was surrounded by a fairly thick connective tissue capsule. A thin enveloping shell of ovarian cortex, showing a number of atretic follicles, could be made out in several areas.

The structure of the tumor was quite cellular and sarcomalike in some places, though even here there was a rather characteristic choppiness of pattern due to the tendency of the cells to arrange themselves in short anastomotic columns. In other parts this cordlike tendency was much more outspoken. These cords were made up of a single or double row of cells whose darkly staining nuclei were placed perpendicularly to the long axis of the column. Between these were collections of much larger, polyhedral cells, with eosin-staining cytoplasm and small round nuclei, which resembled interstitial cells. The cells in the more compact areas were round or fusiform, with heavily staining nuclei of irregular shape and size. A moderate number of mitoses were seen. Large areas of the tumor showed extensive coagulation necrosis.

Postoperative Course.—This could best be summarized in the patient's own words, as expressed in a letter of recent date. "My menstruation returned exactly one month from the day I was operated upon, and has been very regular since. I have been pregnant twice since, but lost both at two months or about that time. The hair has completely disappeared, and there has been a great improvement in my voice, but it is not back to normal yet."

CASE 3.—For the privilege of including this case in my series I am indebted to Dr. A. Giordano, of South Bend, Indiana, who was good enough also to send me a generous portion of the tumor. The patient was a girl of 22 years who had previously been normal, but who one year before operation ceased menstruating. The breasts became very small, the voice became deeper and rather hoarse, and she developed a heavy facial growth of hair, as well as marked hirsutism on the extremities and abdomen. At this time examination by the family physician disclosed an abdominal tumor, which at operation (Sept. 28, 1934) proved to be of ovarian origin.

Pathologic Examination.—The specimen consisted of a slice of tumor tissue, measuring 9 cm. in diameter (presumably the diameter of the tumor) and 3 cm. in thickness. The external surface was of grayish-wrinkled appearance, in places almost resembling pigskin. The cut surface showed numerous cystic spaces, varying from a few millimeters to 3 cm. in diameter. The intercystic tissue was of grayish color, though in one quadrant it was yellowish and firm, with only a few tiny cystic areas.

Microscopically, as in most cases of arrhenoblastoma, wide variations in histologic appearance were seen in different parts of the tumor. In some the structure was quite compact, in others of loose texture, with areas of even myxomatous appearance. In the more solid areas, one could see the characteristic cordlike arrangement of the cells, while in others they formed more substantial columns. The cells were round or spindle, with chromatin-rich nuclei of differing shape. In the peripheral parts of the tumor a frankly tubular pattern was seen, the tubules being lined by epithelium which in some places was very low, in others rather tall and peglike. Islands of cells which histologically resembled Leydig cells were seen here and there, especially in the distinctly tubular portions.

Postoperative Course.—A recent letter from Dr. Giordano informs me that "menstruation was re-established, but the voice still remains masculine and the patient still has to shave regularly. There has been no evidence of recurrence and the patient is still perfectly well" (about three and one-half years after operation).

CASE 4.—On Nov. 9, 1936, Dr. J. P. Lovett of Olney, Texas, kindly sent me slides from a tumor of the left ovary which had just been removed from a girl of 17 years,



Fig. 9.



Fig. 10.

Fig. 9.—Microscopic picture in Case 3, showing characteristic sex-cordlike pattern.
Fig. 10.—Tubular pattern in parts of tumor from Case 3.

and later was good enough to send me a portion of the tumor for further study. I am indebted to him for permission to include this case in the present report. This patient had begun to menstruate at the age of 13, and the periods had been normal until the age of 15, when they became scanty and soon ceased entirely. There had been complete amenorrhea for fifteen months before operation. Marked facial acne was noted. "She developed the contour of a male, the breasts retrogressed, the clitoris became markedly hypertrophic, and the voice became much deeper."

Report of Pathologic Examination.—The tissue consisted only of several small portions of the original tumor, so that no gross description is possible. Microscopically the tumor was composed of strands and masses of rather small cells, with considerable areas of intervening loose connective tissue. The blood vessels were large and numerous. The tumor cells were round or oval, with dark-staining nuclei which varied much in size and shape. In some areas, however, the cells were spindle-shaped. Here and there one found a tendency toward an imperfect tubular pattern,

the lumina being of small caliber, but the characteristic cordlike arrangement was very pronounced, even where there was no evidence of tubules. An occasional mitosis was seen, and small collections of cells suggestive of Leydig cells were also encountered in some parts of the sections.

Postoperative Course.—Three months after operation Dr. Lovett wrote me that the patient had been married two months previously, and was enjoying perfect health, having already gained 15 pounds. The figure had again become rounded, and the abnormal hair growth on both the face and the rest of the body had practically disappeared. The voice was still a trifle husky, though "the patient humorously remarked that she could again sing." The breasts had become larger than those of the average female of her age. The facial acne had disappeared. "The most remarkable feature of this patient," wrote Dr. Lovett, "had been the hypertrophy of the clitoris, which had regressed in size so that it is now not much larger than the average." There was no sign of recurrence of the tumor. More recently Dr. Lovett has informed me that the patient gave birth to a normal full-term child fourteen months after operation.

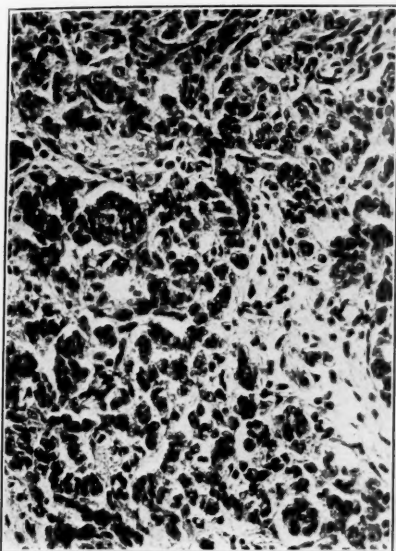


Fig. 11.



Fig. 12.

Fig. 11.—Microscopic appearance of tumor in Case 4.

Fig. 12.—Microscopic picture in Case 5, showing a highly tubular pattern (testicular adenoma) not unlike that of seminiferous tubules, though in many parts (lower right) the tubules are reminiscent of the rete testis. No interstitial cells could be demonstrated in this case.

CASE 5.—For the privilege of studying this case, and including it in this report, I am indebted to Dr. Omer E. Hagebusch and Dr. T. J. Kemp, of St. Louis, Missouri. The patient, aged 40 years, gave as her chief complaints pelvic discomfort and extreme scantiness of menstruation for a number of months. There was no evidence of masculinization manifestations, such as abnormal hair growth, hypertrophy of the clitoris, or deepening of the voice. The patient had had one pregnancy, terminating in early miscarriage in 1931. Examination by Dr. Kemp disclosed a tumor mass in the abdomen, and at operation (Dr. Kemp) on April 23, 1937, a large tumor of the right ovary was revealed. It measured 10 cm. in diameter, and was perfectly smooth and quite symmetrical. The right adnexa were removed. The tumor, on being opened, was found to contain lobulated masses of a brainlike tumor substance attached only over a limited area to the capsule, which was about 2 mm. thick.

Report of Pathologic Examination.—The tissue sent to me by Dr. Hagebusch was a part of the tumor, measuring about 4 cm. in its greatest diameter. The color and

consistency was like that of fixed brain tissue. The surface showed lobulations of about 1 to 2 cm. in diameter.

Microscopically, the tumor is made up dominantly of an adenoma-like tissue, showing large numbers of wide tubular lumina arranged in groups or islands set in a sparse connective tissue substrate. The closely packed tubules are lined with a single layer of large oval or low columnar epithelium, with rather large nuclei and an occasional mitotic figure. The tubules bear a striking resemblance to seminiferous tubules, and in places the lining epithelial cells are not unlike the Sertoli cells of the testis. There is some shedding of the lining epithelium into the lumen of some of the tubules. In a number of areas the tubules are lined by a much lower epithelium, with more abundant interlobular connective tissue, such areas being strongly reminiscent of the rete testis. A few of the tubules are dilated and cystic. No cells which morphologically resemble Leydig cells can be seen in the interstitial tissue.

Postoperative Course.—The patient, according to a recent report, has remained perfectly well since operation, and menstruation has again become normal in character and amount. (Letter from Dr. Hagebusch Feb. 18, 1938, ten months after operation.)

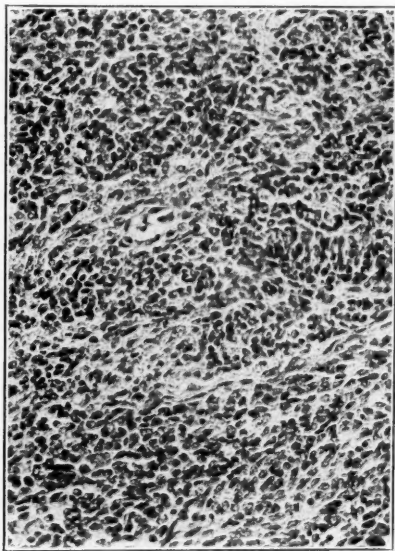


Fig. 13.—Microscopic appearance in Case 6, with rather broad cords of cells shown in this field, though in most parts the tumor cannot be differentiated from sarcoma.

CASE 6.—For the privilege of adding this case to my series I am indebted to Dr. R. L. Gench, Fort Scott, Kansas, and Dr. Ferdinand C. Helwig, of Kansas City, Missouri. The patient, 34 years of age, had had complete amenorrhea for seven months, and three or four months before operation she developed a heavy growth of facial hair, especially on the chin, as well as hirsutism of the extremities and abdomen, where the hair extended from the pubes in a triangular fashion to the umbilicus. She had been obliged to shave regularly. It has not been possible to secure any information as to any changes in the breasts, clitoris, or voice. A unilateral ovarian tumor was removed at operation by Dr. Gench on April 25, 1937.

Report of Pathologic Examination.—The specimen which Dr. Helwig kindly sent me was a rather globular tumor measuring 10 by 9 by 6 cm. The surface was slightly irregular, like that of the normal ovary. The tumor was of even consistency except at one portion, where there was a soft spongy, easily compressible area about 2 cm. in diameter. On section the tumor showed a rather cream-colored slightly granular surface, though in many places the tissue felt gummy, and in the one area above

described, quite spongy. In the center of the tumor there was a whitish area of rather firm fibrous consistency. A few fairly large blood vessels were seen, but there were no cystic areas.

Microscopically, all the sections from many blocks showed in the main what looks like a mixed cell sarcoma. In many places, however, the sarcoma areas were traversed by bundles of spindle cells resembling unstriated muscle. The cells of the sarcoma areas were round or spindle in shape, with large, heavily-staining nuclei. A moderate number of mitoses were seen. In several areas of some of the sections there was a suggestion of tubular pattern, the occasional tubules being lined by a single layer of epithelium. Scattered here and there were larger cells with eosin-staining cytoplasm morphologically resembling interstitial cells. The cordlike arrangement of the cells in some places, with the occasional occurrence of tiny imperfect tubules, would seem to justify the classification of the tumor as a highly indifferntiated sarcomalike variety of arrhenoblastoma.

Postoperative Course.—Dr. Gench reported, on Feb. 12, 1938, that it had not been possible to induce the patient to return for re-examination. She wrote, however, that menstruation returned twenty-eight days after operation, and that she was perfectly well (ten months after operation).

DIAGNOSIS OF ARRHENOBLASTOMA

The appearance, in a previously normal woman, of such defeminization and masculinization phenomena as have been detailed above, together with the presence of a tumor of the ovary, warrants a strong suspicion of arrhenoblastoma. The endocrinopathy which most frequently calls for differentiation is that associated with cortical lesions of the adrenal, since these produce a clinical picture almost exactly like that of arrhenoblastoma. Usually, however, the symptoms are more gradual in development, and no ovarian tumor is palpable. Even though an ovarian neoplasm is present, together with masculinization symptoms, the diagnosis of arrhenoblastoma cannot be considered absolute. I have operated upon a number of such cases in which the ovarian tumor proved to be a simple cystadenoma, with not the slightest trace of arrhenoblastomatous elements even on very complete microscopic study. In such cases, as might have been expected, there was no regression of symptoms after the removal of the tumor, whose existence was simply coincidental in a patient suffering with an adrenal endocrinopathy. I am here discussing those cases, and they are numerous, in which no tumor of the adrenal is palpable, and in which none can be demonstrated by such diagnostic adjuvants as pyelography, pneumoperitoneum, etc.

In this connection I may mention an interesting specimen for which I am indebted to Dr. Victor Bergstrom, of Binghamton, N. Y. The patient, aged 22 years, had had scanty menstruation for three months, and was said to have developed a hoarse voice, marked masculine hirsutism, and atrophy of the breasts. There was no hypertrophy of the clitoris. At operation a large tumor of the ovary was found. Histologic study of many blocks from all parts of the tumor failed to show any evidence of arrhenoblastoma, and, from the presence of areas of cartilage and other alien tissues, it seemed that the tumor should be classified as a teratoma. No chorioepitheliomatous elements could be demonstrated. In response to a recent inquiry Dr. Bergstrom informs me that there has been no change in the patient's characteristics since operation, confirming our view that the masculinization changes were due, not to the ovarian tumor, but to some other endocrine factor, probably of adrenal cortical origin.

The most perfect clinical simulation of arrhenoblastoma, however, is seen in the case of certain rare ovarian tumors which are composed of adrenal tissue. In spite of the infrequency of these neoplasms, it so happens that within little more than a year I have received for examination slides or tissue from 3 instances of this interesting tumor type. These came from Dr. A. Rottino, of St. Vincent's Hospital, New York, Drs. E. Perry McCullagh and Allen Graham, of the Cleveland Clinic, and Drs. H. J. Schattenberg and Hilliard Miller, of Tulane University. While all these cases will later be more fully reported by the observers themselves, they have kindly permitted me to make preliminary brief mention of them in this paper. A glance at the histories will reveal how perfectly these mimic the symptomatology of arrhenoblastoma.

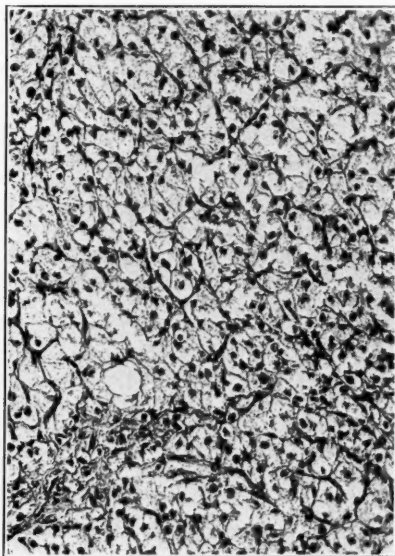


Fig. 14.—Typical adrenal tissue making up ovarian tumor in Case 7.

CASE REPORTS OF ADRENAL TUMORS OF THE OVARY

CASE 1.—(Dr. Rottino.) The patient, aged 24 years, had menstruated normally until the age of 20, when the menses abruptly ceased. She had borne one child six and one-half years before operation. Marked facial hirsutism developed, requiring daily shaving, and there was also a heavy growth over the chest, abdomen, and both upper and lower extremities. There was enlargement of the clitoris, and the voice was slightly husky. At operation (June, 1937), the adrenals were carefully explored and found normal. The right ovary was found to be twice normal in size, and on section a sharply circumscribed orange-colored, roughly spherical nodule was revealed, measuring 3 by $2\frac{1}{2}$ cm. in diameter. It occupied chiefly the medullary portion of the ovary, the cortex being thinned out to form a sort of capsule about the tumor. Microscopically, the tumor showed the typical structure of adrenal tissue, with not the slightest histologic resemblance to arrhenoblastoma. Dr. Rottino states that since the operation "the menstrual periods have returned, the patient has lost her husky voice, she shaves less frequently, and the hairs have become finer in texture and can be easily pulled out."

CASE 2.—(Drs. McCullagh and Graham.) The patient, aged 37 years, had begun to menstruate at 14, the periods always being irregular, with intervals of from two to six months, the flow being sometimes scanty, sometimes profuse. During 1931 there were 12 periods, some 2 weeks apart and quite profuse. Between 1931 and 1934, when she came under observation, there had been only 5 menstrual periods.

The breasts were well developed and not tender. There was moderate hirsutism of the face, upper lip, cheeks, chin, breasts, abdomen, and extremities. The voice was deep, although definitely feminine. The clitoris was markedly hypertrophied, and the labia normal. The cervix was soft and boggy, and the adnexa free from tenderness or masses. The fundus could not be well outlined because of the obesity, but was, apparently, in good position. Her height was 63 inches, and her weight 160 pounds. The blood pressure was 130 systolic and 90 diastolic.

The blood count showed 4,980,000 red cells and 97 per cent hemoglobin. The urinalysis, fasting blood sugar, and blood Wassermann were normal. An x-ray of the sella and the visual fields revealed no abnormality. X-rays of the kidneys, ureters, and bladder were done, because she had chronic left lumbar pain, and showed no abnormality. Bilateral pyelograms were normal. The basal metabolic rate was minus 7 per cent.

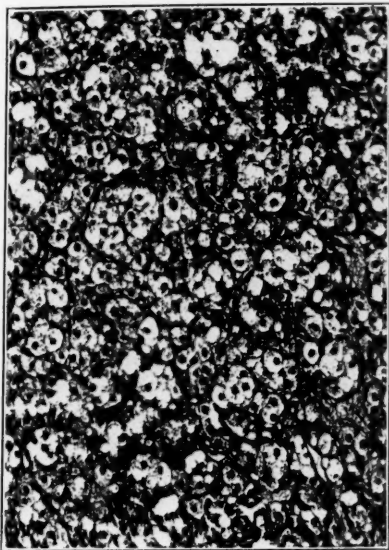


Fig. 15.

Fig. 15.—Microscopic appearance of adrenal ovarian tumor in Case 8.

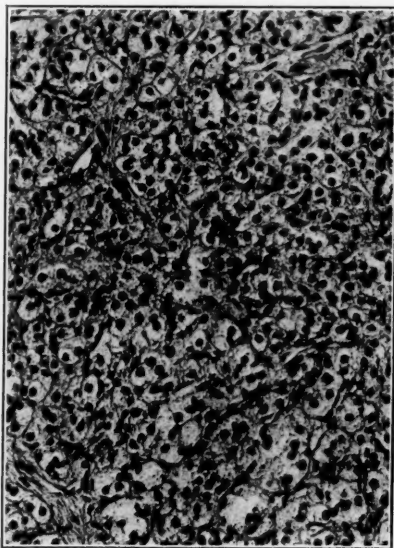


Fig. 16.

Fig. 16.—Microscopic appearance of adrenal ovarian tumor in Case 9.

At intervals of a week 2 estrin assays were done by the Kurzrok method, and showed less than 4 rat units in each of two twenty-four-hour specimens. Two assays were also done on forty-eight-hour specimens for masculinizing hormone by the chloroform extraction method, 2 birds being used for each test, which showed 12 and 4, and 7 and 2 mm. comb growth, respectively. The average normal for men with this test is 10 mm. The Friedman test was negative.

A diagnosis of suspected adrenal tumor was made.

The right adrenal was explored. No evidence of cortical tumor or definite hypertrophy was found. A week later, both ovaries were removed. The right was found at operation to be about 6 cm. in diameter, covered by a firm capsule, containing 6 small hemorrhagic cysts. Section showed it to be made up of a rather yellow homogeneous mass, which appeared to contain connective tissue not resembling ovarian tissue. The left ovary was 4 cm. in diameter and was cystic. The cyst fluid was clear and yellowish.

Report of Pathologic Examination.—Specimen consisted of the major portion of the right and left ovaries. The left ovary weighed 25 gm. and measured 5 by 2.8 by 2.6 cm. It was fairly firm and the external surface was rather irregular due to a few bulging cystic areas along the outer rim. On section, there was an outer compressed rim of ovarian tissue, measuring 4 mm. in thickness. There were a number of follicular cysts in this area. These contained blood-tinged fluid. The major portion of the ovary was occupied by a fairly discrete, firm, oval-shaped mass of tissue. There was a considerable amount of hyalinization present in this tissue and the remainder was composed of moderately firm, yellow, granular tissue. The right ovary weighed 10 gm. and measured 4 by 3 by 2.2 cm. On section, there were a number of follicular cysts present, but there was no tissue resembling that found in the left ovary.

“Microscopically, the right ovary shows numerous, simple, follicular cysts in the cortex and one, fairly large cyst, lined by a single layer of columnar epithelial cells, resting on a dense layer of collagenous, fibrous tissue. There are no other unusual features about the right ovary. Sections of the left ovary show several, small, simple follicular cysts in the cortex, and several primordial follicles. In the central portions of the ovary, there is a large area of tumor tissue consisting of small alveoli containing large, polygonal cells, which have a large amount of vacuolated cytoplasm and relatively small round or oval, deeply staining nuclei. The cytoplasm is finely reticulated and somewhat granular in the less vacuolated cells. The alveoli are separated by a well vascularized, delicate, trabecular tissue stroma. There are numerous areas of dense, hyalinized scar tissue scattered through the tumor. There is no distinct gland formation or tubular formation in any of the sections. There is no distinct capsule between the tumor area and the overlying ovarian cortex.” (Dr. Graham’s note.)

Postoperative Course.—A letter from the patient to Dr. McCullagh nearly three years after the operation stated that her general health was good, except that she was still rather nervous and tired easily. The hair growth was not much changed, and the weight was 134 pounds. Not a single menstrual period had been skipped since operation.

CASE 3.—(Drs. Schattenberg and Miller.) This patient, aged 27 years, had, eight or nine months previously, developed hirsutism, enlargement of the clitoris to 3 or 4 times the normal size, and a marked deepening of the voice. There had been amenorrhea for one year, and the breasts were flat. Clinically, it was thought that she had an arrhenoblastoma of the ovary. A small tumor of the right ovary was actually found at the operation performed by Dr. Miller (Feb. 18, 1938). It was 2 cm. in diameter, entirely within the substance of the ovary, and of golden yellow color. Microscopically the sections showed the tumor to consist of what was apparently typical adrenal tissue, identical in appearance with the two preceding cases. There is not the slightest resemblance to any type of arrhenoblastoma. As to the post-operative course, Dr. Schattenberg informs me that menstruation returned on April 15, about two months after operation, and that there has been definite retrogression of the other symptoms, though only a short time has elapsed since the operation.

Here, then, we have to deal with three adrenal blastomas of the ovary which produced masculinization symptoms identical with those of arrhenoblastoma, and, as with the latter, there was a striking regression of the abnormal manifestations after removal of the tumor. And yet none of these tumors histologically could be mistaken for arrhenoblastoma. The fact that adrenal tumors with this masculinizing capacity can occur in the ovary, and that they produce symptoms similar to arrhenoblastoma, must be taken as evidence of both the embryologic and biologic kinship of the two anlagen.

The whole question of adrenal tumors of the ovary, and particularly of their relationship with the so-called luteomas, is still in a confused state. I have in previous papers expressed doubt that the

mature functioning lutein cell, notoriously a very evanescent structure, could be the source of tumor growth. There is no doubt that certain granulosa cell cancers can exhibit a lutein-like transformation of the constituent cells, and this may be so complete that the tumor might be converted into a lutein-cell tumor. I have seen such a histologic transformation in parts of tumors which primarily are clearly of the granulosa-cell variety, so that there would seem to be no doubt of its possibility.

On the other hand, in most of the tumors which have been reported as luteomas, such an explanation can be ruled out, and I agree with Schiller⁹ that with a very few possible exceptions, these tumors are of adrenal rather than lutein character. Schiller accepts only 3 cases from the previous literature (Schultze-Bingel, Sellheim, Cosaceseo-Drăganescu-Georgescu-Dinischiotu) as probably luteomas. I have been impressed with the fact that in most of the ovarian adrenal tumors, such as the three I have described, and also in the case of adrenal ovarian "rest" reported in 1936 by Saphir and Parker,²⁸ the growths have had the structure of normal adrenal tissue, and that they have not been of the type of the so-called hypernephroma of the ovary. A number of the latter have been recorded, both primary and secondary, and commonly highly malignant. As with the so-called hypernephroma of the kidney, however, sex character alterations are usually absent. In some cases, the explanation of this lies in errors of pathologic diagnosis, for in both the ovary and kidney many tumors formerly diagnosed as hypernephroma are now looked upon as adenocarcinomas. There is no doubt that a certain type of ovarian adenocarcinoma, by the pale staining, large size and frequently alveolar arrangement of its cells, may closely simulate the appearance of adrenal tissue. Careful study of other parts of the tumor will, however, usually show the more or less typical gland architecture characteristic of adenocarcinoma.

Whether the genuinely adrenal tumors of the ovary are to be looked upon as adrenal rests or as adrenal adenomas, in the sense in which adenoma is now employed to designate localized collections of functionally over-active cells of various endocrine glands, is difficult to say. Aberrant adrenal tissue is not infrequently observed, such rests being especially frequent along the course of the ovarian or spermathecal vessels. In the ovary itself they are rare. They are not so infrequent, however, in the broad ligament, and I have encountered two cases in which small islands of what is apparently typical adrenal tissue occur near the ovarian hilum (Fig. 17). In neither of these patients, however, was there the slightest suggestion of masculinization changes. The mere presence of normal adrenal tissue in the ovary therefore would probably not in itself seem sufficient to explain such changes as were observed in the three cases I have mentioned, and, since the islands were of considerable size and evidently neoplastic, they are probably best interpreted as adrenal adenomas of the ovary. Neither in the histologic picture nor in the clinical course is there any suggestion of malignancy.

There is still a woeful lack of knowledge concerning the nature of the unquestionably important relationship between the adrenal cortex and the gonads, and also the mechanism of the genital changes so characteristically seen with virilizing tumors of the adrenal cortex, in the well-known corticogenital syndrome. Recent studies upon the so-called androgenic zone of the adrenal suggest that perhaps a persistence of this zone, which in the human being disappears within the first year of life, may be concerned with the development of the corticogenital syndrome, and Broster and Vines,²⁹ as well as other authors, have made efforts to identify the cells of the androgenic zone by a special fuchsinophile stain. In the present state of our knowledge, it is scarcely worth while elaborating on this point, or in discussing various other hypotheses as to the mechanism involved in the corticogenital syndrome.³⁰

As regards arrhenoblastoma, we are even more in the dark as to the underlying cause for the neoplastic awakening of potentially testicular elements in the ovarian medulla. In passing, however, it may be mentioned that in at least one reported case, that of Gnassi, several separate arrhenoblastomas were present in one ovary, suggesting that some extraovarian factor might have been responsible for this multicentric neoplasm. One would naturally think of the adrenal as most likely to be the source of this extraovarian stimulus, but thus far there has been no histologic evidence to substantiate such a view.

From a diagnostic standpoint, it is clear that even with a definite history of defeminization and masculinization, associated also with the finding of an ovarian neoplasm, there is no way as yet to differentiate with any precision between adrenal ovarian tumors and arrhenoblastomas. Hormone studies may perhaps make this possible in the future. Thus far there is little or no information of significance as to the urinary hormone characteristics of either tumor type. There is little reason, moreover, to think that adrenal adenomas of the ovary would exhibit the high estrogen urinary concentration which Frank looks upon as characteristic of malignant cortical tumors of the adrenal.

SUMMARY

This paper is based primarily on the study of 11 cases of arrhenoblastoma, including the 6 new cases here reported. This group raises the total number of cases in the literature from 45 to 51, although instances of this interesting tumor type are being recorded with increasing frequency. The characteristic biologic effect of this neoplasm is to produce defeminization and masculinization phenomena. Chief among the former are amenorrhea, retrogression of the mammary glands, and loss of the feminine contour. Of the masculinization effects, the most striking are hirsutism, deepening of the voice, and hypertrophy of the clitoris. Removal of the tumor is followed by a return to normality, though this may not always be complete. In a small minority

of cases, even though the tumor is clearly an arrhenoblastoma from a histologic standpoint, abnormal sex changes may be almost or entirely absent.

The proper basis for the microscopic diagnosis of these tumors is a knowledge of the early embryology of the gonads, and only in this way can one appreciate the very different histologic appearance encountered in different tumors and often in different parts of the same tumor. All gradations are seen between a structure closely simulating that of normal testis (testicular adenoma), to pictures showing only incomplete efforts at tubular formation, to those of sarcoma-like appearance. The fact that all these variations may be seen in different tumors, producing the same biologic effect, and, for that matter, in different parts of the same tumor, is strong evidence not only of their kinship, but also of the probable correctness of Meyer's original hypothesis that the origin of arrhenoblastoma is from certain male-directed cells persisting in the medulla of the ovary, particularly in the region of the rete ovarii.

The clinical and pathologic characteristics of the tumor have been described, stress being laid upon the fact that regression of the symptoms is of rather crucial importance in the substantiation of the diagnosis. While the development of masculinization phenomena in a previously normal woman, coupled with the presence of an ovarian tumor, justifies a strong suspicion of arrhenoblastoma, such a diagnosis cannot be considered absolute, as has been discussed in the paper. It is not possible, for example, to eliminate the possibility of the rare ovarian tumor composed of adrenal tissue, of which 3 cases are reported in this paper. The clinical syndrome of this tumor type and that of arrhenoblastoma may be almost identical, though there is not the slightest histologic resemblance. It seems quite probable that the adrenal may in some as yet unknown way be linked up with arrhenoblastoma, or at any rate that it may play a part in the production of the characteristic symptomatology of this tumor.

REFERENCES

- (1) Sedlacek, E.: Arch. f. Gynäk. 153: 276, 1933. (2) Kleine, H. O.: Arch. f. Gynäk. 157: 410, 1934. (3) von Szathmary, Z.: Arch. f. Gynäk. 157: 170, 1934; 164: 478, 1937. (4) Phelan, G. W.: AM. J. OBST. & GYNEC. 27: 748, 1934. (5) Gnassi, A. J.: Ibid. 31: 135, 1936. (6) McLester, J. B.: Arch. Int. Med. 57: 773, 1936. (7) Baldwin, L. G., and Gafford, J. A.: Endocrinology 20: 373, 1936. (8) Young, H. H., and Te Linde, R. W.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, 1937, Williams & Wilkins Co., p. 322. (9) Schiller, Walter: Arch. f. Gynäk. 156: 513, 1933. (This case was reported also by Förderl: Monatsch. f. Geburtsh. u. Gynäk. 106: 54, 1937.) (10) Schockaert, J. A.: Bruxelles-méd. 16: 525, 1936. (11) Miller, J. R.: AM. J. OBST. & GYNEC. 34: 680, 1937. (12) Norris, E. H.: Am. J. Cancer 32: 1, 1938. (13) Behrend, M., and Levine, S.: Arch. Surg. 33: 392, 1936. (14) Walters, W., Wilder, R. M., and Kepler, E. J.: Ann. Surg. 100: 670, 1934. (15) Novak, E., and Long, J. H.: J. A. M. A. 101: 1057, 1933. (16) Moots, C. W.: AM. J. OBST. & GYNEC. 1: 864, 1921. (17) Popoff, N. W.: Arch. Path. 9: 31, 1930. (18) Spielman, F.: AM. J. OBST. & GYNEC. 27: 517, 1933. (19) Taylor, J. M., Wolfermann, S. J., and Krock, F.: Surg. Gynec. Obst. 56: 1040, 1933. (20) Meyer, R.: Beitr. z. Path. Anat. u. z. Allg. Path. 84: 485, 1930; Ztschr. f. Geburtsh. u. Gynäk. 98: 543, 1930; Zentralbl. f. Gynäk. 54: 2374, 1930; AM. J. OBST. & GYNEC. 22: 697, 1931; Arch. f. Gynäk. 145: 2, 1931. (21) Pick, L.: Berl.

Klin. Wehnschr. 42: 502, 1905. (22) *Fischel, A.*: Ztschr. f. d. ges. Anat. u. Entwicklungsgesch. 100: 331, 1933. (23) *Streeter, G. L.*: Personal communication. (24) *Novak, E.*: J. A. M. A. 105: 413, 1935. (25) *Cadiz, R., and Lipschütz, A.*: Arch. f. Gynäk. 153: 593, 1933. (26) *Wagner, G. A.*: Ztschr. f. Geburtsh. u. Gynäk. 98: 130, 1930. (27) *Krediet, G.*: Arch. f. Gynäk. 158: 22, 1934. (28) *Saphir, W., and Parker, M. L.*: J. A. M. A. 107: 1286, 1936. (29) *Broster, L. B., and Vines, H. W. C.*: Adrenal Cortex, A Surgical and Pathological Study, London, 1933, H. K. Lewis & Co. Ltd. (30) *Grollman, A.*: The Adrenals, Baltimore, 1936, Williams & Wilkins Co.

DISCUSSION

DR. JAMES RAGLAN MILLER, HARTFORD, CONN.—Since 1916 at the Hartford Hospital we have observed 10 granulosa-cell tumors, 2 Brenner tumors and 2 arrhenoblastomas. We have seen no adrenal ovarian tumors. Neither of the arrhenoblastomas have shown any signs of masculinization; on the contrary, one of the cases showed bleeding in the menopause. Consequently I believe Dr. Novak is right in taking the attitude that the term "arrhenoblastoma" should not be confined merely to those cases which show signs of masculinization.

Since both of our cases showed no signs of masculinization, I feel inclined to consider Halban's theory. He believed that the hormones of the adrenal cortex and of the arrhenoblastoma with which we are here concerned are not specific male activators but may activate either gonad. He assumed also that when a female shows masculinization effects she does so because at birth she was a potential hermaphrodite and the effect is caused by the stimulation of male gonadal rests in her ovary. If there be no male tissue capable of functional response she may show precocious puberty or accentuated female characteristics in much the same manner as do the granulosa-cell cases. Such effects are reported in the presence of adrenal cortical tumors. Halban's theory is quite opposed to the conception of Grollman who postulates a distinct "androgenic" or "X" zone of adrenal subcortical cells to which he attributes the masculinizing hormone.

The role of the interstitial cell is not yet fully established, for it is certain that masculinizing effects are less often observed where the interstitial cells are best developed. These cells are best seen in fetal life and in the undescended testis and are not conspicuous at puberty when one would expect them to be at their highest state of development if they control secondary sex characteristics.

END RESULTS IN 400 CASES OF PLACENTA PREVIA*

ALBERT H. ALDRIDGE, B.S., M.D., F.A.C.S., AND
THOMAS J. PARKS, B.S., M.D., F.A.C.S., NEW YORK, N. Y. .

*(From the Obstetrical Services of the Woman's Hospital, and the Sloane
Hospital for Women)*

IMPLANTATION of the placenta in the lower uterine segment still constitutes one of the most serious complications to be met in the practice of obstetrics.

Facts regarding the development of our scientific knowledge of placenta previa, the theories as to its causation, the symptomatology, and the accepted methods of treatment are too familiar to require discussion.

Accumulated experience has established facts which, in the treatment of placenta previa, cannot safely be disregarded. These facts may be briefly summarized as follows:

1. Implantation of the placenta in the lower uterine segment tends to interfere with proper engagement of the presenting part and is not infrequently associated with an abnormal presentation of the fetus.
2. Post-partum control of bleeding from the placental site depends upon firm contraction of the superimposed uterine musculature.
3. The lower uterine or passive segment of the uterus has very little hemostatic contracting power. Conditions associated with placenta previa further reduce physiologic hemostasis and predispose to excessive bleeding from the placental site.
4. Abnormal adherence of a placenta attached to the lower uterine segment occurs occasionally and may be a serious complication at time of delivery.
5. Atony of uterine musculature, which may follow excessive blood loss and surgical shock, tends to increase bleeding from the uterus and especially from the placental site.
6. Conditions associated with implantation of the placenta in the lower uterine segment predispose to cervical injury, rupture of the uterus, and infection during the course of labor and delivery.

Although this condition has been known since the time of Hippocrates, perhaps the most significant advance in the treatment of placenta previa has occurred in the past quarter of a century. Within this period of time, there has developed a better appreciation of the importance of consistently treating placenta previa in accordance with sound surgical principles. These principles include: (1) Prevention of infection. (2) Prevention of unnecessary hemorrhage and adequate replacement of blood loss. (3) Prevention and treatment of surgical shock by blood transfusion and other methods. (4) Avoidance of unnecessary trauma.

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

Estimation of the relative value of the various methods of delivery and treatment of placenta previa must depend upon the extent to which they allow reasonable adherence to these surgical principles.

In the past few years, a striking reduction in maternal and fetal mortality from placenta previa has occurred in most obstetric clinics. This has been possible because:

1. Routine procedures have been put into effect from the time symptoms appear until delivery has been accomplished, thereby reducing the incidence of infection from all the usual sources.
2. The technique of blood transfusion has been improved until it is now a relatively simple, safe procedure.
3. In addition to blood transfusion, other effective methods for the treatment of surgical shock have been made readily available.
4. The incidence of undesirable results, from the trauma of vaginal delivery, has been reduced through perfection of the technique of operative obstetric procedures.
5. Improvements in the technique of cesarean section have increased the safety of suprapubic delivery and have allowed its more extensive use.

Many obstetricians have adopted cesarean section as an almost routine procedure for the treatment of central placenta previa and as the method of choice for the treatment of selected cases of partial and marginal varieties.

The advantages claimed for delivery by cesarean section are that:

1. Delivery without allowing the lower uterine segment to dilate tends to retain the limited hemostatic power which it possesses.
2. Delivery is quickly accomplished, reducing blood loss before and during delivery. Hemorrhage can be more promptly and positively controlled.
3. Cesarean section, particularly with incision in the lower uterine segment, allows inspection of the placental site. Active bleeding from sinuses can be controlled by suturing and packing under direct vision.
4. Undesirable or dangerous complications resulting from trauma of vaginal delivery are avoided.
5. Maternal morbidity and infection, the result of manipulation and contamination by vaginal procedures, is eliminated.
6. Fetal mortality, especially in central placenta previa, is strikingly reduced.

As difference of opinion still exists as to the most suitable method of delivery for the various types of placenta previa, it was decided to conduct a combined study of the end results of treatment of 400 such cases occurring at the Woman's Hospital in the past twenty-one years and at the Sloane Hospital for Women in the past seventeen years.

Table I shows the number and incidence of cases of placenta previa occurring at these two institutions within the periods of time stated above.

TABLE I. INCIDENCE OF PLACENTA PREVIA

	NUMBER OF DELIVERIES	PLACENTA PREVIAS	INCIDENCE
Woman's Hospital	25,388	185	1 in 137
Sloane Hospital	33,933	215	1 in 158
Total	59,321	400	1 in 148

As a uniform classification of the various types of placenta previa has not been universally adopted by obstetrical authorities, it will be necessary to state that the classification which was used for this study was as follows:

1. *Marginal* where a part of the placenta was implanted in the lower uterine segment but the edge did not extend beyond the margin of the internal os.
2. *Partial* when part of the opening of the cervix was covered by placenta.
3. *Central* when the internal os of the cervix was completely covered by placenta.

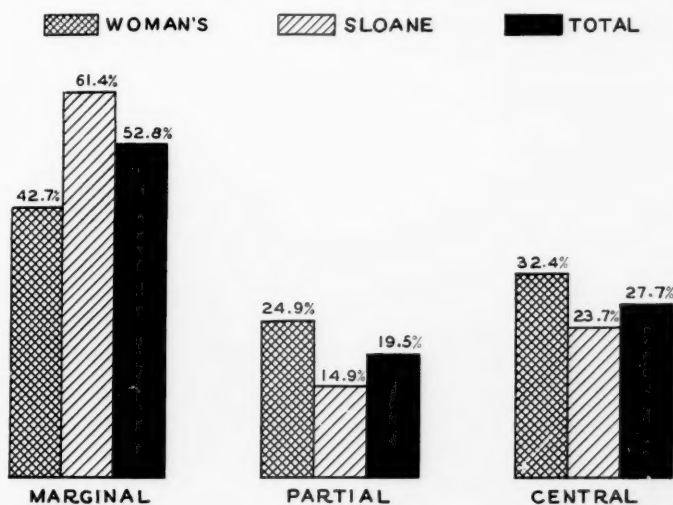


Fig. 1.—Classification by type in 400 cases of placenta previa.

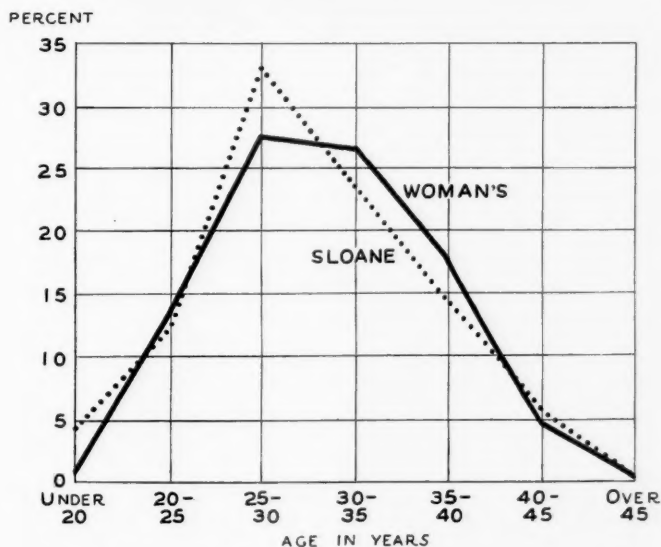


Fig. 2.—Age incidence in 400 cases of placenta previa.

Classification was based upon physical findings at the time the condition was diagnosed. In many cases findings by vaginal examination were checked by recorded findings when cesarean section was done.

According to the classification outlined above, the 400 cases studied were classified as shown in Fig. 1.

It is interesting to note that approximately one-half (52.8 per cent) of the cases were classified as marginal, one-fifth (19.5 per cent) as partial, and one-fourth (27.7 per cent) as central placenta previa.

Fig. 2 shows the incidence of all cases studied in relation to age. At both institutions the maximum incidence occurred in the twenty-five- to thirty-year age groups.

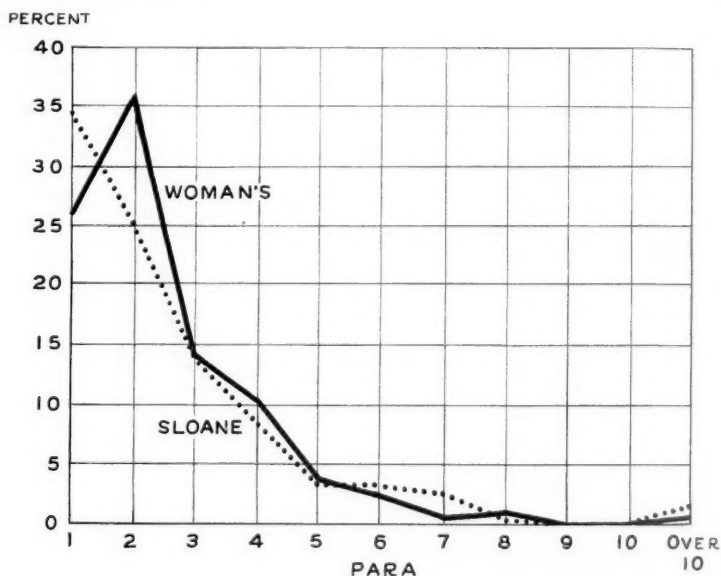


Fig. 3.—Parity in 400 cases of placenta previa.

Table II shows the age groups with maximum incidence in relation to type of placenta previa.

Fig. 3 shows the incidence of cases studied in relation to parity.

In the Woman's Hospital series the maximum percentage of cases of all types were at or near term with their second pregnancy, and in the Sloane series the greatest incidence occurred during the first pregnancy.

TABLE II. AGE GROUPS WITH MAXIMUM INCIDENCE IN 400 CASES OF PLACENTA PREVIA

TYPE OF PREVIA	AGE GROUP	
	WOMAN'S HOSPITAL	SLOANE HOSPITAL
Marginal	30-35	25-30
Partial	25-30	25-30
Central	35-40	25-30
Total	25-30	25-30

Table III shows the parity groups with maximum incidence in relation to type of placenta previa.

TABLE III. PARITY GROUPS WITH MAXIMUM INCIDENCE IN 400 CASES OF PLACENTA PREVIA

TYPE OF PREVIA	PARITY GROUP	
	WOMAN'S HOSPITAL	SLOANE HOSPITAL
Marginal	Para ii	Para i
Partial	Para ii	Para ii
Central	Para i	Para i
Total	Para ii	Para i

Of the patients treated 67.5 per cent were multiparous women. Multiparity has been considered an important predisposing factor in placenta previa. It is interesting to note that about one-third (32.4 per cent) of the cases treated occurred in women at or near term with their first pregnancies. The rather high incidence of placenta previa occurring in the first and second pregnancies may in part be due to

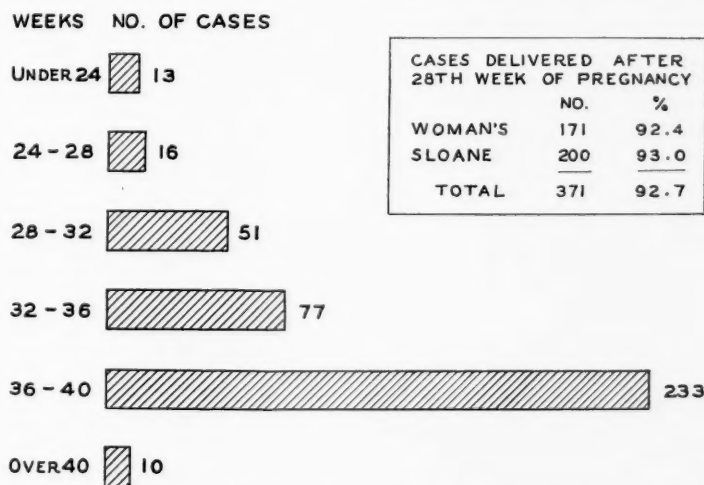


Fig. 4.—Period of gestation at time of delivery in 400 cases of placenta previa.

the fact that, in admitting patients to the obstetric services at both hospitals, preference is given to patients having their first or second child and patients having previous difficult confinements.

Fig. 4 is a summary of the incidence of cases studied in relation to the periods of gestation at time of delivery.

The relative high incidence of abnormal presentation, as shown in Fig. 5, confirms the fact that implantation of the placenta in the lower uterine segment may interfere with engagement of the presenting part and complicate delivery by vagina.

Table IV shows the distribution of cases in relation to type of delivery employed. The number of deaths occurring after the various methods of delivery is also recorded.

Voorhees' bags were used to induce labor and to control hemorrhage in approximately one-half (52.5 per cent) of the cases delivered by vagina.

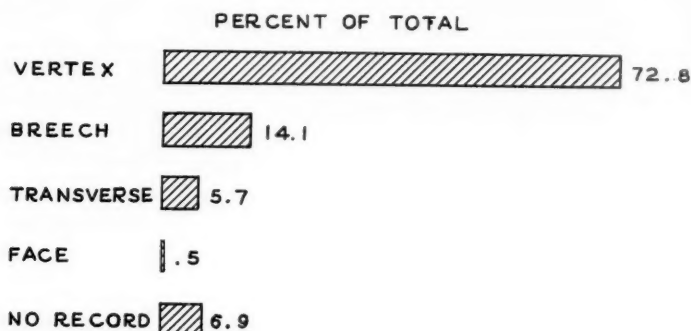


Fig. 5.—Presentation when symptoms appeared in 400 cases of placenta previa.

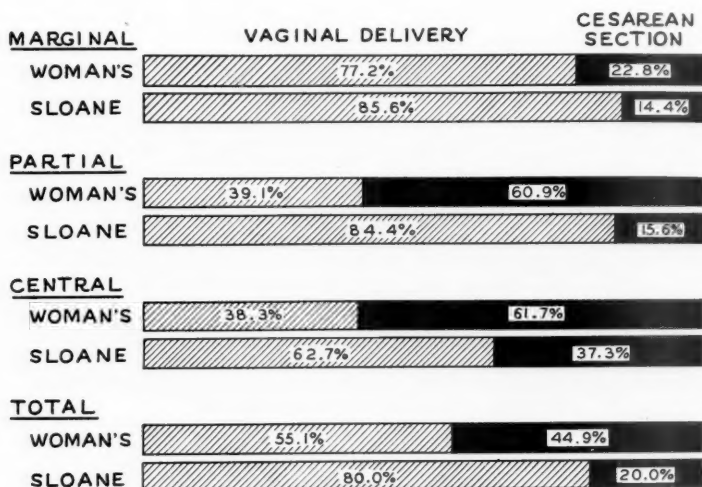


Fig. 6.—Incidence of vaginal delivery vs. cesarean section in 400 cases of placenta previa.

In Fig. 6 the incidence of vaginal deliveries vs. cesarean sections is shown.

It will be noted that in the Woman's Hospital series approximately 60 per cent of both partial and central placenta previa cases were delivered by cesarean section. At the Woman's Hospital 44.9 per cent of all cases were delivered by cesarean section, while at Sloane only one-fifth (20.0 per cent) was delivered by this method.

TABLE IV. MATERNAL MORTALITY BY METHOD OF DELIVERY IN 400 CASES OF PLACENTA PREVIA

METHOD OF DELIVERY	NUMBER OF DELIVERIES	MATERNAL DEATHS
Vaginal delivery—Total	274	13
Normal	82	2
Breech	40	3
Forceps—Low	27	0
Mid	17	0
High	5	0
Version and breech extraction	102	8
Vaginal hysterotomy	1	0
Cesarean section—Total	126	8
Classical	65	4
Low flap	57	3
Peritoneal exclusion	1	1
Porro	3	0
Total	400	21

TABLE IVA. MARGINAL AND PARTIAL PLACENTA PREVIA—INDICATIONS, IN ADDITION TO PLACENTA PREVIA, FOR DELIVERY OF 70 CASES BY CESAREAN SECTION

COMPLICATIONS	WOMAN'S HOSPITAL		SLOANE HOSPITAL	
	MARGINAL	PARTIAL	MARGINAL	PARTIAL
1. Feto-maternal disproportion:				
Contracted pelvis	5	4	6	1
Large babies (weight 8 pounds 11 ounces to 9 pounds 4 ounces)	1	2		
2. Previous pelvic operations:				
High amputation cervix		1		
Pregnancy after Watkin's interposition		1		
Retroversion operation for sterility and repeated abortion	1			
Previous cesarean section	1		1	
3. Abnormal presentation	1	2	2	1
4. Elderly primiparas (37-40 years)	2	5	2	
5. Previous complicated deliveries	1	1	1	
6. Cardiac disease	2	3		
7. Toxemia of pregnancy	2		1	
8. Fibroids			2	
9. Sterilization			1	
10. Safety of mother and baby:				2
Moderate to profuse bleeding before or during labor		7	1	
Cervix unsuitable for bag	2	1	2	
Fetal distress		1		1
Total number of cesarean sections	18	28	19	5

In Table IVA it will be noted that at the Woman's Hospital only 11 (24 per cent) of the 46 cases of marginal and partial placenta previa without other complications were delivered by cesarean section. At Sloane only 6 (25 per cent) of the 24 cases of marginal and partial placenta previa delivered by cesarean section were free of other complications.

In other words in both series approximately three-fourths of such patients had complications which in themselves were acceptable in-

dications for cesarean section or which would have seriously complicated delivery by vagina.

Table V is a summary of the incidence of maternal deaths in cases delivered by vagina as compared to those delivered by cesarean section.

TABLE V. MATERNAL MORTALITY RATE IN 400 CASES OF PLACENTA PREVIA

	VAGINAL DELIVERY			CESAREAN SECTION		
	NO. OF CASES	DEATHS	PER CENT	NO. OF CASES	DEATHS	PER CENT
<i>Woman's</i>						
Marginal	61	1	1.6	18	1	5.5
Partial	18	2	11.1	28	1	3.6
Central	23	3	13.0	37	4	10.8
Total	102	6	5.9	83	6	7.2
<i>Sloane</i>						
Marginal	113	2	1.8	19	0	0.0
Partial	27	2	7.4	5	0	0.0
Central	32	3	9.4	19	2	10.5
Total	172	7	4.1	43	2	4.6

Although cesarean section is gaining in popularity as a method of delivery for placenta previa, it would appear from the results of this series that delivery by vagina is a safer procedure. However, from a study of the facts regarding the treatment of the patients that died following cesarean section, it is obvious that the deaths which occurred were due not so much to the operation itself as to poor judgment in applying this method of delivery.

Eight of the 21 deaths in the series followed delivery by cesarean section. Of these 8 deaths, 4 were from hemorrhage and shock, 3 from sepsis, and 1 from acute yellow atrophy of the liver. By present-day methods of handling these cases it seems possible that any or all of these deaths might have been prevented.

The results of delivery by cesarean section, in more recent years, have been much more satisfactory as shown in Table VI. This table

TABLE VI. TREND OF MATERNAL MORTALITY IN 185 CASES OF PLACENTA PREVIA AT WOMAN'S HOSPITAL

	NUMBER OF CASES	DEATHS	PER CENT
Vaginal delivery			
1917-1923	34	4	11.8
1924-1930	47	2	4.2
1931-1937	21	0	0.0
Total	102	6	5.9
Cesarean section			
1917-1923	6	2	33.3
1924-1930	19	2	10.5
1931-1937	58	2	3.4
Total	83	6	7.2
Total			
1917-1923	40	6	15.0
1924-1930	66	4	6.1
1931-1937	79	2	2.5
Total	185	12	6.5

shows the striking improvement in results of treatment in three successive seven-year periods at the Woman's Hospital. It is believed that better results have been due to more extensive use of cesarean section and to prevention and better treatment of hemorrhage and shock.

Table VII is a summary of the incidence and causes of maternal deaths after delivery by vagina and cesarean section.

TABLE VII. CAUSES OF MATERNAL DEATHS IN 400 CASES OF PLACENTA PREVIA

	WOMAN'S	SLOANE	TOTAL
<i>Deaths After Vaginal Delivery</i>			
No. of deliveries	102	172	274
Cause of death			
Hemorrhage and shock	3	5	8
Embolism	3*	0	3
Septicemia	0	2	2
Total—Number	6	7	13
Per cent	5.9	4.1	4.7
<i>Deaths After Cesarean Section</i>			
No. of deliveries	83	43	126
Cause of death			
Hemorrhage and shock	3†	1	4
Acute yellow atrophy	1	0	1
Acute general peritonitis	1	0	1
Septicemia and paralytic ileus	1	1	2
Total—Number	6	2	8
Per cent	7.2	4.6	6.3

*Other complications: Acute nephritis 1; phlebitis 1.

†Other complications: Acute yellow atrophy 1; Myocarditis, chronic 1.

Table VIIA is a summary of facts regarding patients that died.

Study of the records of the 21 patients who died shows that 12 died of hemorrhage and shock. Ten of these patients had no other complications. Of the 12 patients, 8 were delivered by vagina and 4 by cesarean section. One patient, delivered by cesarean, had chronic myocarditis, and had been hospitalized during pregnancy for cardiac decompensation. However, the immediate cause of death in this case was hemorrhage and shock. Another patient delivered by cesarean section died following post-partum extraperitoneal hemorrhage, estimated at 300 c.c. at autopsy. Although she had acute yellow atrophy she was apparently progressing satisfactorily until the post-partum hemorrhage occurred. In other words more than one-half of the deaths in the series were the result of hemorrhage and shock.

One of these 12 patients was transfused before delivery and one immediately after cesarean section. In none of the remaining 10 cases was preparation started for transfusion until the patient had bled excessively during or after delivery and had developed some degree of surgical shock.

With present-day handling it seems reasonable to consider all of the 12 deaths, as a result of hemorrhage and shock, as possibly preventable.

Three of the 21 deaths were from emboli in patients delivered by vagina. One occurred at the end of delivery and was probably unavoidable. A second patient died from embolism on the eighth post-partum day after having developed acute nephritis from iodoform packing left in the uterus for six days. The third death was due to embolism on the twenty-fourth post-partum day in a patient who had an infected perineal wound and phlebitis. It should probably be considered a death from sepsis.

TABLE VIIA. SUMMARY OF MATERNAL DEATHS

CASE	TYPE OF PREVIA	AGE	PARA	PERIOD OF GESTATION (WEEKS)	METHOD OF DELIVERY	COMPLICATIONS AND CAUSE OF DEATH	TIME OF DEATH	CRITICISMS OF TREATMENT
<i>Woman's Hospital Series</i>								
1	Central	39	vi	40	Bag, version and breech extraction	Hemorrhage and shock	Died on table	No preparation for transfusion until patient was in shock from hemorrhage
2	Central	No record	vi	36	Bag, version and breech extraction	Hemorrhage and shock	3 hr. after delivery	In serious condition before delivery. No preparation made for transfusion
3	Marginal	41	ii	40	Version and breech extraction	Hemorrhage and shock	1 day	No preparation for transfusion. Profuse hemorrhage
4	Central	33	v	42	Low flap cesarean section	Transverse presentation. Hemorrhage and shock. Baby 11 pounds 10 ounces	20 min. after delivery	Transfused at end of operation. Control of bleeding by packing and delay of operation for treatment of shock might have been a life-saving measure
5	Central	35	i	38	Low flap cesarean section	P.P. Extraperitoneal hemorrhage, shock, acute yellow atrophy liver. Autopsy	9 hours after delivery	Transfusion 9 hours after delivery. Earlier transfusion might have controlled predisposition to bleeding with acute yellow atrophy
6	Marginal	27	i	36	Low flap cesarean section	Shock and circulatory collapse. Myocardial disease with decompensation in A.P. period	Died day of operation	Went into shock during operation. Preparation for transfusion started after patient was in serious condition
7	Partial	26	No record	35	Bag, version and breech extraction	Pulmonary embolism	Died on table	Death accidental. Probably not preventable
8	Central	37	v	32	Packing, bag and breech delivery	Acute nephritis. Iodoform poisoning. Coronary embolism. Autopsy	8 days	Packing 6 post-partum days unnecessary, probably fatal to sensitive patient

TABLE VIII.—CONT'D

9	Partial	33	i	38	Breech delivery	Phlebitis. Pulmonary embolism. Infected wound	24 days	In spite of marked secondary anemia, no transfusion until fifteenth p.p. day
10	Central	32	v	28	Classical cesarean section	Acute yellow atrophy. Suppression urine. (26 ounces in 8 p.p. days)	8 days	With symptoms of acute yellow atrophy delivery was delayed too long in order to get living child
11	Partial	32	ii	36	Classical cesarean section	Acute general peritonitis	6 days	Potentially infected on admission. Classical cesarean section, unwise method of delivery
12	Central	30	iii	40	Cesarean section peritoneal exclusion	Uremia. Septicemia. Paralytic ileus	8 days	Excessive bleeding before and at delivery, estimated over 2,000 c.c. One transfusion 550 c.c.

<i>Sloane Hospital Series</i>								
1	Marginal	32	i	40	Bag, packing, version and breech extraction	Lacerated cervix. Hemorrhage and shock	40 hours after delivery	Delivered when cervix was four fingers dilated. Transfusion not given until day after delivery
2	Central	22	i	40	Bag and packing. Classical cesarean section	Hemorrhage and shock	2 hours after delivery	Elective cesarean section justifiable with male pelvis and central previa. Transfusion before operation might have prevented fatal hemorrhage and shock
3	Central	22	i	28	Spontaneous delivery	Marked secondary anemia. Hemorrhage and shock.	7 hours after delivery	Serious condition during labor. Not given transfusion until one hour after delivery
4	Central	29	iv	36	Bag, packing, version and breech extraction	Hemorrhage and shock	Day of delivery	Version through cervix dilated 6 cm. (profuse hemorrhage). One transfusion, 400 c.c., inadequate replacement of blood loss

TABLE VIIA.—CONT'D

CASE	TYPE OF PREVIA	AGE	PARA	PERIOD OF GESTATION (WEEKS)	METHOD OF DELIVERY	COMPLICATIONS AND CAUSE OF DEATH	TIME OF DEATH	CRITICISMS OF TREATMENT
5	Central	22	ii	40	Bag, version and breech extraction	Contracted pelvis. Large baby 8 pounds 7 ounces. Hemorrhage and shock. Ruptured uterus. Autopsy	Day of delivery	Poor condition on admission. Three transfusions total 1810 c.c. Delivery before full cervical dilatation. Cervix and uterus not examined for injury. Delivery by cesarean justifiable and safer
6	Marginal	30	iv	28-30	Breech extraction	Long, rigid cervix. Prolonged labor (118 hr.). Hemorrhage and shock.	On table	Three transfusions, total 2,100 c.c. Breech extraction without full dilatation of cervix. Trachelorrhaphy. Bag might have helped cervical dilatation. Cesarean section might have been justifiable
7	Partial	20	i	36	Dührssen's incisions Breech extraction	Profuse hemorrhage at operation. Sepsis and exhaustion	11 days	Mother febrile (99°-100.2°) during 6 days' observation. Intrauterine death of fetus (3 pounds 2 ounces). Bleeding had ceased. To await spontaneous delivery might have been safer
8	Central	33	ii	40	Classical cesarean section	Sepsis (paralytic ileus). Immediate cause of death incompatible blood?	6 days	Profuse bleeding before delivery. No transfusion until sixth p.p. day. Earlier and repeated transfusions might have prevented fatal outcome.
9	Marginal	26	iv	29	Bag, spontaneous delivery	Temperature at 104° end of delivery. Septicemia (Hemolytic streptococcus)	14 days	Infected on admission. Six transfusions. Death probably inevitable

One of the 21 deaths was the result of acute yellow atrophy of the liver. In view of the toxic symptoms delivery was postponed too long in an effort to get a viable baby.

Five of the 21 deaths were definitely the result of sepsis. Of the 2 septic deaths after vaginal delivery, one had symptoms of infection on admission and death was probably inevitable. The other occurred after Dührssen's incision and breech extraction in a case which failed to respond satisfactorily to attempts at induction. With a febrile (99° to 100.2°) mother during six days of observation before induction was attempted, intrapartum death of a 3 pound 2 ounce fetus and cessation of hemorrhage, it might have been safer to wait for spontaneous cervical dilatation. Two septic deaths followed classical cesarean section. One of these patients had an adherent placenta and profuse bleeding at delivery but no transfusion until the sixth post-partum day. The other classical cesarean section was unwisely chosen as the method of delivery in a patient with a definite potential infection. Vaginal delivery or Porro cesarean section would have been safer.

It is evident from the records that the patients who developed sepsis could have had much better post-partum care. In 4 of the 5 cases replacement of blood loss was inadequate or was delayed until sepsis developed. It seems obvious that adequate replacement of blood loss may be as important in preventing dangerous post-partum complications as in the prevention of surgical shock. A depleted post-partum patient should be transfused, and repeatedly transfused if necessary, for the prevention of complications as well as for their treatment.

Table VIIB shows the outcome of babies delivered by vagina vs. cesarean section in the three types of placenta previa. In the Woman's Hospital series with its higher incidence of cesarean section, a total of 76.3 per cent of viable babies survived as compared to 64.7 per cent in the Sloane series.

Table VIII is a summary of the survival of viable babies after vaginal delivery vs. cesarean section.

From a study of end results it is difficult to formulate an accurate opinion of the success of the various methods of treatment for any obstetric condition. This is true because results are usually based upon survival of patients treated.

It is obvious from this series of cases that most of the patients that died as well as many that survived were carried through labor, delivery, and the post-partum period with too narrow a margin of safety.

The outstanding fault of treatment was the failure to provide adequate replacement of blood loss. The condition of many patients at time of delivery was such that even moderate additional blood loss was sure to throw them into dangerous or fatal shock. Others were actually in shock when delivered by vagina or cesarean section.

Patients with placenta previa are usually admitted to a hospital with a history of painless bleeding either at or before the onset of labor. Excessive bleeding can almost invariably be controlled by packing and bags for a sufficient period of time to allow blood transfusion before delivery and preparation for subsequent transfusions. Delivery of a patient with marked anemia or while in shock invites

TABLE VII B. FETAL MORTALITY. SURVIVAL OF VIABLE BABIES AFTER DELIVERY BY VAGINA *vs.* CESAREAN SECTION

	WOMAN'S			SLOANE		
	MARGINAL	PARTIAL	CENTRAL	MARGINAL	PARTIAL	CENTRAL
<i>Delivery by Vagina</i>						
No. of deliveries	61	18	23	113	27	32
No. of babies	62	19	23	114	27	32
	(1 set of twins)	(1 set of twins)				
Nonviable babies	7	2	5	7	0	6
Viable babies	55	17	18	107	27	26
Stillbirths	3	3	6	28	13	17
Neonatal deaths	8	3	6	4	2	5
Survived	44	11	6	75	12	4
Survived, viable babies in percentages	80.0	64.7	33.3	70.0	44.4	15.3
Survived all types by vaginal route, 67.7					56.8	
<i>Delivery by Cesarean Section</i>						
No. of deliveries	18	28	37	19	5	19
No. of babies	18	29	37	19	5	20
		(1 set of twins)				
Nonviable babies	0	1	0	0	0	0
Viable babies	18	28	37	19	5	20
Stillbirths	0	2	1	0	0	3
Neonatal deaths	1	1	7	0	0	0
Survived	17	25	29	19	5	17
Survived, viable babies in percentages	94.4	89.2	78.3	100.0	100.0	85.0
Survived all types after cesarean section, 85.5					93.11	

TABLE VIII.—SURVIVAL OF VIABLE BABIES AFTER VAGINAL DELIVERY *vs.* CESAREAN SECTION IN 400 CASES OF PLACENTA PREVIA

TYPES OF PLACENTA PREVIA	WOMAN'S HOSPITAL		SLOANE HOSPITAL	
	VAGINAL DELIVERY	CESAREAN SECTION	VAGINAL DELIVERY	CESAREAN SECTION
Marginal	80.0	94.4	70.0	100.0
Partial	64.7	89.2	44.4	100.0
Central	33.3	78.3	15.3	85.0
Total	67.7	85.5	56.8	93.2

disaster. Experience proves that delivery under such conditions to save the child is unjustifiable.

Patients with organic disease complicated by pregnancy and placenta previa present problems to test the skill and judgment of the most competent obstetrician. Such patients must be individually considered in order to decide upon the most suitable time and method of delivery.

Potentially or actually infected patients are serious risks regardless of the method of delivery. If they are to be delivered by the abdominal route, Porro cesarean section rather than the classical or low flap types of operation should be employed. Although we have had no experience with extraperitoneal cesarean section in this type of

case, it is possible that it may eventually offer a conservative means of delivery for at least the potentially infected cases.

To summarize it may be stated that:

1. Placenta previa constitutes one of the most serious complications to be met in obstetric practice.

2. Patients should be treated according to sound surgical principles for the prevention of infection, unnecessary hemorrhage, surgical shock, and trauma.

3. Patients should be prepared as carefully for vaginal delivery or cesarean section as for any major surgical operation.

4. Blood transfusion provides the most effective means for the prevention and treatment of surgical shock. Other means of treating shock should be readily available in every obstetric hospital to protect patients while preparations for blood transfusion are being made.

5. Delivery by vagina or cesarean section of a patient in shock or seriously depleted by hemorrhage should not be undertaken until adequate replacement of blood loss has been accomplished.

6. Complications resulting in dangerous hemorrhage may be unexpectedly encountered during delivery. Provision for blood transfusion during operation may prevent disaster.

7. Cesarean section offers a valuable means of delivery of patients with central placenta previa and selected cases of partial and marginal placenta previa.

8. Placenta previa frequently occurs in patients who have physical conditions which either constitute acceptable indications for cesarean section or which may seriously complicate delivery by vagina.

9. Fetal mortality is strikingly reduced in patients delivered by cesarean section.

10. Blood transfusion to combat anemia and to improve the general physical condition of patients following delivery may reduce the incidence and danger of post-partum complications.

11. Conditions associated with placenta previa demand hospital treatment for safety.

DISCUSSION

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—During the past five years there were 8,410 deliveries at the Methodist Episcopal Hospital in Brooklyn, with 38 cases of placenta previa, giving an incidence of 1 in 221.

Our methods of management are similar to those of the last seven years of Dr. Aldridge's, namely, simple rupture of the membranes, the use of the Voorhees' bag or cesarean section. In these 38 cases there were no maternal deaths. There were 15 fetal deaths, a mortality of 31.5 per cent. We can justifiably correct this rate, because there were two macerated fetuses and five nonviable prematures, so that the corrected fetal mortality is 21 per cent.

Taking the cesarean sections separately there were 7 of the classical and 3 of the low flap type, a total of 10 cases with no maternal mortality and one fetal death. This baby was stillborn although the fetal heart was thought to have been heard shortly before operation.

I agree with Dr. Aldridge that we need a more accurate classification and would suggest subdividing the partial group by adding the terms Partial I, where the

placenta covers 50 per cent or less of the cervical canal; and Partial II, 50 per cent or more. The marginal and central types do not need to be subdivided.

Ude and Urner have recently recommended cystograms in the diagnosis of placenta previa. We have used this method at the Methodist Episcopal and Long Island College Hospitals in well over 100 cases. This method is important and gives some valuable information, but it is not always absolutely accurate. If the x-ray shows a sinking down of the head in the lower segment, one can definitely say there is no placenta previa. On the other hand, if there is a space of from 1.5 to 2.5 cm., it may or may not be placenta previa.

These patients should under proper precautions, have a pelvic examination through the vagina. In Brooklyn there is some agitation for not examining placenta previa cases. There are conditions, of course, where vaginal examinations should not be made, but examination is obligatory in the vast majority of cases. We teach and practice that "without a correct diagnosis there can be no intelligent treatment."

Minimizing trauma is most important, and of course, it is much more important to prevent infection than to treat it. Likewise, the prevention of shock is more important than its treatment, and if present it should be treated immediately. The longer shock is present the less likely the patient is to survive. Heat, morphine, and blood transfusion are essential. As an illustration, only last week we had a patient with a ruptured uterus in profound shock. In forty-five minutes she had been given 2,000 c.c. of blood and had had a hysterectomy. The next morning she sat up and ate her breakfast.

There is no question but that cesarean section is gradually coming into its own. There is also no question that one must have the conditions that call for section.

DR. NORRIS W. VAUX, PHILADELPHIA, PA.—Dr. Aldridge's review indicates clearly the very definite improvement in maternal and fetal mortality from this complication of pregnancy, in two outstanding maternity hospitals in the United States, in the last ten years.

I approve the use of vaginal examination in cases of placenta previa, provided no undue risk is entailed and proper preparation of the patient and attendants has been strictly enforced. It is imperative that all preparations and equipment necessary for combating secondary hemorrhage following vaginal examination, be at hand.

I have been for years an advocate of the more radical procedure of operative delivery. Yet I fully realize that all cases of placenta previa are not necessarily close to a well-equipped institution where this method of procedure can be safely carried out. I therefore wish to emphasize the importance of conservative treatment in all such instances.

I am glad that your attention has been called to the added risk associated with vaginal, as compared with abdominal, delivery in cases of placenta previa. Cesarean section does, without a doubt lessen the risk of uterine infection as well as trauma of the lower uterine segment and of the cervix. The close relationship of the placental site in the lower uterine segment to the vagina increases the risk of any vaginal manipulation. Cesarean section also eliminates the danger of rupture of the uterus at the placental site.

It is interesting to note that in 33,012 patients delivered in the Jefferson Maternity and the Philadelphia Lying-In Hospitals, in approximately ten years, there were 166 patients with proved placenta previa (marginal, partial, or central), an incidence of one placenta previa case in every 198 deliveries, which is somewhat less than the incidence in either the Woman's Hospital or the Sloane Maternity. There were 11 maternal deaths in our series, a maternal mortality of 6.6 per cent. One of these cases was moribund on admission and died undelivered. In comparing the vaginal delivery deaths (4.9 per cent) in placenta previa with those delivered by the abdominal route, the percentage of cesarean section deaths (8.3 per cent) is somewhat higher. Maternal mortality rose very definitely in those individuals in whom there was a serious delay in replacement of blood loss when secondary hemor-

rhage occurred, and this possibly was the factor in the resultant fatal surgical shock and collapse. It would seem to me, therefore, that prompt replacement of blood to combat the surgical shock, regardless of vaginal or abdominal delivery, should not be long postponed after the initial hemorrhage.

I cannot agree that the method of choice in delivering placenta previa by the abdominal route is the low flap cesarean section. A more pronounced blood loss is likely to occur following this type of incision while a fundal or classical incision, which is far removed from the placental site, may give better results relative to the separation of placenta after delivery and the primary and immediate spontaneous involution of the uterus.

It is advisable to accept all painless bleeding in the last trimester of pregnancy as that of placenta previa until it has been proved otherwise, and as such the patient should be immediately hospitalized, for the sake of safety. Upon admission to a well-equipped institution, replacement of blood loss should be the first treatment instituted, and that without delay. The condition in which the patient is found at the time of admission and the type of placenta previa determined by examination, should be the indications for either temporary delay or prompt surgical intervention. No patient in surgical shock from blood loss associated with placenta previa should be considered an operative risk until the treatment instituted for surgical shock has become effective.

DR. F. C. GOLDSBOROUGH, BUFFALO, N. Y.—I want to emphasize the importance of correct diagnosis because of an experience I had recently in seeing a patient with a ruptured uterus in her second pregnancy. She had had, she said, a placenta previa in her first delivery. On account of a slight blood-tinged discharge she had been rushed into the hospital, and with a diagnosis of placenta previa, delivery was made by cesarean section. The proper diagnosis was the slight show of the onset of labor.

A second case was sent in with a diagnosis of placenta previa. As there was no hemorrhage on admission she was kept under observation. There was no further hemorrhage, the patient went to term and was delivered normally. The diagnosis in this case was decidua polyposa. In some hospitals she would have had an immediate cesarean, without a correct diagnosis.

DR. FRED L. ADAIR, CHICAGO, ILL.—When one attempts to classify according to the relation of the placenta to the cervical canal or os, there is a great deal of variation, dependent upon the stage of labor and the time the symptoms develop. Naturally the exposure of the placenta varies with the amount of dilatation. We have tried to simplify the classification as much as possible and to recognize only two groups of placenta previa, on the basis of the conditions found at the time the first symptoms develop. We recognize the type where the os is covered and the type where the os is not covered at that time. This serves as a fundamental basis for deciding the type of treatment required. In our classification there are only the complete and the incomplete types.

A point worthy of emphasis, in the early diagnosis, is the warning hemorrhage. Many cases of placenta previa have a show of blood and if one pays attention to this slight bleeding which occurs in the last trimester, without any other symptoms, one can usually forestall more serious hemorrhage. With any bleeding the patient should be brought to the hospital, if possible, and carefully examined in order to rule out a placenta previa. About one-fourth to one-third of these cases with warning bleeding have a placenta previa, and they are treated promptly.

There is no stereotyped form of treatment. The condition and the parity of the mother and the status of the fetus must all be taken into consideration. A cesarean section is not indicated where the life of the fetus is not at stake. Where the fetus is nonviable or dead or already in a serious condition, cesarean section should not be undertaken, as the condition, so far as the mother is concerned, can be treated successfully without it in most cases.

I will not quarrel over the relative merits of direct or indirect transfusion. The important thing is to transfuse the patient immediately and as often as necessary. About one-fourth of our cases are transfused. Cesarean section is done in about one-fourth to one-third of our cases. Willett forceps and the Braxton Hicks version are used. Usually the bag is ruled out except where the life of the fetus is already extinct or of no particular value. The lower segment cesarean section is used more frequently in our hospital than the upper segment or classical type. The advantages of the one in giving access to the placental site, and of the other in keeping away from the placental site are admitted. Both methods give good results. While our results have been questioned in some quarters, nevertheless we have had practically no maternal mortality, and we believe that it can be reduced to practically nil, that the fetal mortality should not exceed 20 per cent uncorrected, and that the corrected mortality should be somewhere around 6 per cent.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—In determining the type of treatment, one should perhaps not attach so much importance to the degrees of placenta previa as to the condition of the cervix. Partial placenta previa with a rigid cervix may be a more serious condition than a complete placenta previa with a soft and retracted cervix. Therefore, I believe that a careful vaginal examination is called for in all cases and that the determination of treatment should depend upon the condition of the cervix more than upon the actual degree of placenta previa.

ENDOMETRIOSIS*

A CLINICAL AND SURGICAL REVIEW

VIRGIL S. COUNSELLER, M.D., ROCHESTER, MINN.

(From the Division of Surgery, the Mayo Clinic)

JUST eighteen years ago Dr. Sampson⁹ presented before this Society his observations on 23 patients with what he designated as "perforating hemorrhagic cysts" of the ovary and stated that, from these hemorrhagic cysts, pelvic adenomas took their origin. He expressed the opinion that he could not be sure that the ovarian hematomas were the only cause of ectopic adenomas. One¹⁰ year later he stated to this Society that ectopic pelvic adenomas originated also from menstrual elements extruded from the uterus through the oviducts and from tubal epithelium which become implanted on the ovary and other pelvic structures. He suggested the term "endometriosis" to designate this pathologic entity. This term has been generally accepted by gynecologists and pathologists.

Many students of the subject have not accepted Sampson's theory regarding the etiology of this disease but, nevertheless, a great debt is due him for stimulating so much interest in it. Most of the papers on the subject have dealt with theories of development, pathologic studies, the distribution of the lesions and the subjective symptoms, and relatively few have dealt with the results of treatment. Read and Roques (1929), Wharton (1929), Keene and Kimbrough (1930), Smith (1929), Cattell (1936), and Pemberton (1937) reviewed their clinical findings and published their results of radical and conservative surgical treatment. Since endometriosis is primarily a surgical disease, the methods involved in its management can be evaluated better and a clearer conception of its clinical importance can be brought about by publication of the results of treatment.

Masson reviewed the cases of 576 patients with endometriosis who were treated at the Mayo Clinic between 1923 and 1934. To this series I wish to add 308 additional cases of patients treated subsequently up to and including 1937. I will then discuss the entire series in somewhat greater detail and evaluate the results of conservative treatment.†

The generally accepted idea of endometriosis is of an abnormal growth of endometrial tissue in an ectopic position. Graves stated that the use of the term "endometriosis" assumes the acceptance of Sampson's theories of etiology. Blair Bell mentioned the term "endometrioma," which indicates tumor formation. In the present series of cases adeno-

*Read at the Sixty-third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1933.

†I am greatly indebted to my assistant, Dr. R. E. Bedard, and to Dr. J. Berkson, of the Statistical Department, for their careful study of our case records and the resulting data.

myomas of the uterus have been included under the general head of endometriosis, which will explain the high incidence of involvement of the uterus.

AGE INCIDENCE

Endometriosis is a disease that occurs principally during the reproductive period, the greatest number of patients being in the fourth and fifth decades of life. The fact that it is seen early in the third decade, however, makes it of increasing importance. Our youngest patient was 21 years of age, the oldest 73 (Table I).

TABLE I. ENDOMETRIOSIS: 1923-1937, 884 PATIENTS

AGE DISTRIBUTION

AGE YEARS	NUMBER	PER CENT
20-29	61	6.9
30-39	272	30.8
40-49	443	50.1
50-59	99	11.2
60-69	8	0.9
70+	1	0.1
Total	884	100.0
Mean age		41.9 years
Youngest patient		21 years
Oldest patient		73 years

Seven hundred and fifteen patients (80.9 per cent) were between 30 and 50 years of age; 61 (6.9 per cent) were between 20 and 30, and 108 (12.2 per cent) were beyond 50. In this last group the lesions were mostly adenomyomas of the uterus, and the surgical treatment for this older group obviously was complete hysterectomy.

LOCATION OF THE LESIONS

The distribution of the lesions followed the same general pattern as given by previous authors who included adenomyomas of the uterus under the heading of endometriosis. The uterus was the most common site of involvement, there being 640 lesions of this organ and the cervix. The ovary was next with 120 lesions. In the group of 108 cases of diffuse endometriosis, it was impossible to give a

TABLE II. ENDOMETRIOSIS: 1923-1937, 884 PATIENTS

ANATOMIC LOCATION OF LESIONS

LOCATION	NUMBER	PER CENT OF PATIENTS*
Uterus	618	69.9
Cervix	22	2.5
Ovary (probably not complete)	120	13.6
Rectovaginal septum	27	3.0
Ligaments of uterus	22	2.5
Sigmoid, rectosigmoid, or rectum	24	2.7
Pelvic peritoneum	44	5.0
Vaginal wall	17	1.9
Fallopian tube	27	3.0
Umbilicus	6	0.7
Ileum	2	0.2
Appendix	1	0.1
Bladder	2	0.2
Diffuse	108	12.2

*More than one organ affected. The total, therefore, does not add to 100 per cent.

specific location to the lesion. Other sites of involvement were the rectovaginal septum in 27 instances, the umbilicus in 6 and the bladder in 2. Twenty-four lesions involved the sigmoid, rectosigmoid or rectum, and 44 involved the pelvic peritoneum (Table II).

DYSMENORRHEA

The clinical symptoms of endometriosis are variable and are determined largely by the location of the masses and the number of regions involved. Dysmenorrhea of the acquired type, with some degree of progression, is very suggestive of the disease. We at the clinic are convinced that in girls in the second and third decades at least, endometriosis is in many cases responsible for pelvic pain, although the lesions are not firm enough to palpate either vaginally or rectally. I rather suspect that in many such cases the pain is due to endometrial growths within the myometrium, as depicted in Fig. 1. This patient, aged 22 years, had been treated for five years for extreme dysmenorrhea without effect and the family had requested

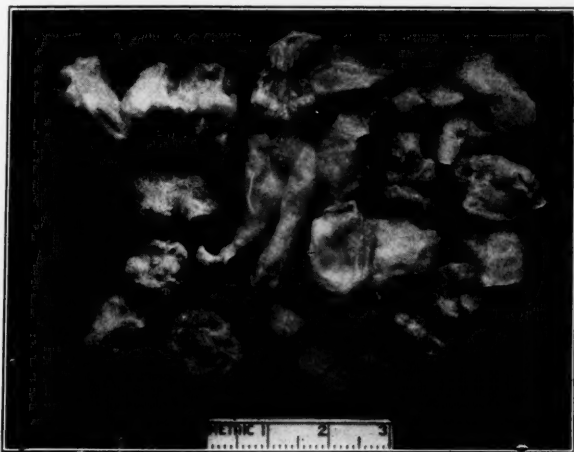


Fig. 1.—Multiple adenomyomas.

that the uterus be removed. At operation, multiple endometrial growths were removed and presacral resection was performed. This was followed by complete relief of pain and by normal menstruation.

Fixation of the uterosacral ligaments and rectovaginal septum usually results in pain of a bearing-down type and, in some cases, in a desire to defecate. These symptoms begin before menstruation is initiated and abate somewhat after the onset; in many cases, however, a dull aching pain is present after the flow ceases. As the disease progresses the duration of the pain increases, so that in the most severe cases patients may not be free from discomfort at any time. Patients presenting such a history usually require radical surgical treatment. In our recent series of 308 cases, in which the data are more complete, 46.8 per cent of the patients had dysmenorrhea, of whom 39.6 per cent had increasing pain and 24 per cent of the entire group had had no pain (Table III). Keene and Kimbrough found that 49.1 per cent of their patients gave a history of increasing dysmenorrhea and that 40 per cent gave no history of pain. Donald has stated that acquired dysmenorrhea was noted in 50 per cent of his cases. It was of interest that 18.7 per cent of our patients with menstrual pain volunteered the information that this pain was definitely worse on exertion. This seemed to be significant since it occurred in cases of extensive involvement.

TABLE III. MENSTRUAL ABNORMALITIES: 308 PATIENTS
(RECENT SERIES, 1935-1937)

	NUMBER	PER CENT OF TOTAL CASES
Menstrual abnormality:		
Menstrual abnormality (any type)	247	80.2
No menstrual abnormality	32	10.4
No information	29	9.4
Pain:		
Pain with menses	144	46.8
Pain increasing	57	39.6*
Pain worse on exertion	27	18.7*
Pain worse on defecation	21	14.6*
Pain worse on urination	7	4.9*
No pain with menses	74	24.0
No information	90	29.2
Menstrual disturbance:		
Menorrhagia and/or metrorrhagia	202	65.6
No menorrhagia or metrorrhagia	48	15.6
No information	58	18.8

*Based on 144 patients with pain.

ASSOCIATED PELVIC DISEASE

Menstrual disturbances are extremely difficult to evaluate, if one attempts to be at all accurate in attributing them to endometriosis, since 54.5 per cent of the 308 patients in the recent series had leiomyomas of sufficient size to account for such irregularity (Table IV). Furthermore, 60 per cent of the patients had lesions

TABLE IV. ASSOCIATED PELVIC DISEASE: 308 PATIENTS
(RECENT SERIES 1935-1937)

	NUMBER	PER CENT OF CASES*
Leiomyoma	168	54.5
Chronic cystic oophoritis	161	52.3
Simple cyst	24	7.8
Corpus luteum cyst	19	6.2
Atrophic oophoritis	12	3.9
Cystadenoma	7	2.3
Carcinoma of ovary	3	1.0
Tubo-ovarian abscess	2	0.6
Carcinoma of uterus	1	0.3
Carcinoma of cervix	1	0.3

*A single patient may have had more than one pathologic condition. The total therefore adds to more than 100 per cent.

of the ovaries other than endometriosis which might also have been responsible for the menstrual disturbance. We are of the opinion that it is reasonable to state that endometriosis per se does not produce disturbances in menstruation, although endometrial adenomas within the uterus itself probably do in some instances. In this series of 308 patients, 65.6 per cent had menorrhagia, metrorrhagia, or both (Table III), which is approximately the same percentage as that stated for the number of associated pathologic lesions of the uterus and ovary (Table IV).

PREVIOUS SURGICAL PROCEDURES

Since endometriomas occur in laparotomy wounds following operations on the uterus, it occurred to us that trauma as a direct result of operation on the pelvic organs or as a result of manipulation of the organs at the time of operation might

well be an etiologic factor in the subsequent production of endometriosis in the pelvic structures. In our recent series of 308 cases, 167 patients (54.2 per cent) had been subjected to previous pelvic operations, but it was not possible to determine in many instances the reason for the operation. Of these, 56.9 per cent underwent some type of surgical procedure on the uterus or adnexa, 12.6 per cent had dilatation and curettage and perineal surgery, and 30.5 per cent had undergone appendectomy or some other abdominal operation. Whether these procedures were performed for pelvic pain or whether they may have been one of the factors in initiating the endometrial process is impossible to say. The high incidence of previous surgical interference, however, is certainly suggestive (Table V).

TABLE V. PREVIOUS SURGICAL PROCEDURES: 308 PATIENTS
(RECENT SERIES 1935-1937)

	NUMBER	PER CENT
Previous surgical treatment	167	54.2
Involving cutting uterus, tube, or ovary	95	56.9*
Dilatation and curettage and perineal surgery	21	12.6*
Appendectomy or other abdominal surgery	51	30.5*
No previous surgical treatment	114	37.0
No information	27	8.8
Total	308	

*Per cent of 167 patients who had had previous surgical treatment.

DIAGNOSIS

The clinical diagnosis of endometrial lesions is rarely made in more than 20 per cent of the cases because of the multiplicity of associated pathologic lesions of the uterus and ovary which may themselves account for the patient's symptoms. There are certain symptoms, however, which, if present, should direct attention to the possibility of endometriosis even though associated lesions are present; for example, an acquired dysmenorrhea of the progressive type occurring in a woman particularly between the ages of 25 and 45. This pain will vary in character depending on the site of the lesion. Adenomyomas of the uterus not infrequently extend through and involve the posterior wall of the bladder, giving rise to vesical symptoms associated with menstruation. This experience will usually be mentioned by the patient without any leading questions by the examiner. Similarly, adenomas involving the cul-de-sac or rectal shelf are usually productive of such rectal disturbances as pain on defecation or rectal pressure, both of which seem to be definitely associated with the initiation of menstruation. In cases of diffuse involvement of the pelvic tissues and rectal shelf, there is a characteristic discomfort which I have not seen mentioned by previous authors; this is pelvic "soreness" brought about by exertion near or during menstruation. It is especially noticeable on walking or riding in such vehicles as buses, streetcars, or automobiles for any considerable distance. When patients complain of sterility and have rather pronounced dysmenorrhea, endometriosis should be excluded.

Endometriosis of the umbilicus presents very little difficulty in diagnosis, such lesions being characterized by their tenderness, enlargement, and discoloration at the menstrual periods. The same is true of lesions in laparotomy scars, particularly following cesarean section, although in the latter instance a sinus may discharge blood coincidentally with menstruation. There may be periodic discharges of blood from the umbilicus of patients who have not had previous operations. Keene and Kimbrough called our attention to a very important point in connection with bloody discharging sinuses subsequent to operations on the uterus: The sinus may connect directly with the uterine cavity, from which blood may be discharged, without the presence of an endometrioma.

Objective evidence of endometriosis is best ascertained through bimanual examination. The most positive evidence is the detection of small nodules in the cul-de-sac on rectal examination. Tenderness is usually out of all proportion to that seen

in cases of chronic inflammatory lesions, especially if the examination is made near the beginning of menstruation. If nodules are also felt behind the cervix or in the posterior vaginal vault, the diagnosis of endometriosis is more nearly certain.

Palpation of the uterosacral ligaments by rectal examination is of distinct value, because they are usually shortened irregularly and are extremely tender. The induration of pelvic inflammatory disease, particularly of the postabortal type, is firmer and more extensive than is encountered in endometriosis.

In the presence of large leiomyomas and tarry cysts, the diagnosis of endometriosis is more difficult to make. In the case of young patients without uterine tumors but with fixed retroversion associated with an increasing dysmenorrhea and without a history of acute pelvic infection, there is presumptive evidence of endometriosis.

As has been said, very little evidence of the presence of endometriosis can be obtained from the character of the menstrual disturbance in view of the fact that such disturbances can be more accurately attributed to an associated uterine or ovarian lesion. Further proof of this lies in the fact that most patients with endometriosis but without associated uterine lesions do not have menstrual irregularities. In our recent series of 308 cases a preoperative diagnosis of endometriosis was made in forty-five instances.

TREATMENT

Since the epochal work of Sampson and of the many others who have investigated the disease thoroughly, it is definitely established that the syndrome produced by endometriosis is dependent on ovarian function. A rather general rule can therefore be stated that removal of ovarian function will cause these lesions to become quiescent and in some instances to disappear. A few exceptions might be made, however, in the case of adenomyomas of the uterus following the menopause. Other factors producing activity of such adenomyomas may be accounted for by malignant ovarian tissue.

Since in most cases endometriosis occurs during the reproductive period, conservative surgical principles with regard to preservation of either the menstrual or reproductive function, or both, must be employed. We at the clinic feel that the upper age limit for conservative procedures is between 37 and 40 years. However, the extent of the lesions and their location are of more importance in selecting the type of operation perhaps than is the age of the patient. For example, if a patient at the age of thirty has a diffuse endometriosis involving the sigmoid, both adnexa and the uterus, she will be better off if a radical operation is performed.

It has been our observation that when it is necessary to perform radical hysterectomy for endometriosis before the menopause, the patients do not experience the severe menopausal symptoms that those patients do who undergo a similar operation for conditions other than endometriosis.

Conservative methods carry a more favorable prognosis when lesions are confined to the adnexa on one side and to a few serosal implants which can be easily excised. In the cases of younger patients with a longer history of dysmenorrhea and in which endometriosis is encountered at operation we have, in addition to conservative treatment, performed presacral resection with the idea in mind that if there were recurrences the patients might not experience the dysmenorrhea which was the original predominating symptom. By this means such patients might carry on in comparative comfort until later in life or until further symptoms justified destruction of ovarian function by surgical means or by irradiation.

In our combined series of 884 cases, 162 patients were treated by conservative procedures, 701 by radical procedures, and a few by radium and roentgen rays (Table VI). When the lesions were diffuse, and particularly when there was considerable fixation of the lower uterine segment, even though the adnexa were not extensively involved, it was our opinion that the risk of recurrence following any conservative procedure was too great. Those patients who had involvement of the rectovaginal septum were treated in the great majority of instances by radium, be-

TABLE VI. ENDOMETRIOSIS: 1923-1937, 884 PATIENTS

TREATMENT	NUMBER	PER CENT OF CASES
Conservative:*		
With presacral resection	19	2.2
Without presacral resection	143	16.2
Radical	701	79.3
Radium	17	1.9
Roentgen	2	0.2
Roentgen and radium	2	0.2
Total	884	100.0

*Operations conserving menstrual function.

cause the surgical risk of excising this particular lesion is too high when it is considered that such patients can be treated satisfactorily by destroying ovarian function by radium. In two instances in which there was a definite history of post-abortal infection, roentgen therapy was employed.

Of the total of 162 conservative surgical procedures in addition to local excision, a tubal operation was employed in 9 cases, oophorectomy alone in 19, salpingo-oophorectomy in 51, local excision in 77, and bowel resection in 6, with or without uterine suspension and with or without presacral resection. Myomectomy was performed in 26 cases (Table VII). This group of 162 patients comprises only 18.4

TABLE VII. SURGICAL PROCEDURES IN 162 CASES IN WHICH PATIENTS WERE TREATED CONSERVATIVELY

PROCEDURE	TOTAL		UTERINE SUSPENSION				WITH PRESACRAL RESECTION	
			WITH		WITHOUT		NO.	%
	NO.	%	NO.	%	NO.	%		
Tubal operation	9	5.6	4	8.7	4	4.1	1	5.3
Oophorectomy	19	11.7	8	17.4	6	6.2	5	26.3
Salpingo-oophorectomy	51	31.5	14	30.4	37	38.1		
Local excision*	77	47.5	20	43.5	44	45.4	13	68.4
Bowel resection	6	3.7			6	6.2		
Total	162†	100.0	46	100.0	97	100.0	19	100.0

*Local excision of endometrial tissue only. In the cases of the other surgical procedures listed, there was also excision of endometrial tissue.

†Myomectomy, which was performed in 28 cases, is not listed in this table.

per cent of the total, which indicates that we have been more radical in our surgical management of the disease than is shown by the report of previous authors. Our selection of cases for conservative management, however, seems justified by the fact that we have had only a small number in which it was necessary to submit the patients to secondary surgical procedures or to radium therapy. Further justification lies in the fact that patients who have already undergone previous pelvic operations, of which there were 167, were unwilling to assume the risk of recurrence. The average age of the group of patients treated conservatively was 33.8 years.

The question of fertility in endometriosis is of considerable importance. It is our observation that if the disease has existed over a long period, and if the symptoms are severe, the possibility of subsequent pregnancy should be quite remote. In the cases of those patients with secondary sterility, the onset of the disease frequently dates back a short time subsequent to delivery, giving cause to believe that the pregnancy or delivery may have been an exciting factor in its production or that the pregnancy or delivery may have reactivated a pre-existing endometriosis. Our information with regard to fertility is derived from the cases of the 162 patients who were treated conservatively and about whom we have fairly accurate information both before and after the pelvic operation (Table VIII). This informa-

TABLE VIII. FERTILITY: 162 PATIENTS TREATED CONSERVATIVELY

	NUMBER	PER CENT
Unmarried	31	19.1*
Married	131	80.9
No pregnancy	42	32.1†
One live birth	18	13.7
Two or more live births	34	26.0
Miscarriages only	22	16.8
No information	15	11.4

*Based on 162 patients.

†Based on 131 married patients.

tion impresses us as being of more value in cases in which we can subsequently follow the patients with regard to fertility than for the entire group, the majority of whom underwent radical operation.

Thirty-one of these 162 patients were unmarried, 131 were married. Our figures for fertility are accordingly based on these 131 patients in whom one could expect pregnancy under normal conditions. In this group there was no pregnancy, or an absolute sterility in 42 cases, or 32.1 per cent; 18 patients or 3.7 per cent, had 1 live birth, 34, or 26 per cent, had 2 or more living births, and 22, or 16.8 per cent, had only miscarriages. We were unable to obtain information in 15 cases, or 11.4 per cent. The incidence of pregnancy, therefore, for this group was 56.5 per cent. The incidence of miscarriage was extremely high, which is presumptive evidence that endometriosis is a very potent factor in it.

Seven patients were known to have become pregnant after such conservative treatment. Of these, 4 had 1 child each, 1 had 2 children, 1 had 4 children, and 1 had a miscarriage, giving a total of 10 children. It should be noted, however, that of the 162 patients who were treated conservatively, 64 were not traced in respect to subsequent pregnancies, 10 were more than 40 years of age at the time of operation, 18 were unmarried, and 15 were sterilized by operation, so that in only about 55 cases could one reasonably expect a report of pregnancy.

RESULTS OF CONSERVATIVE SURGICAL TREATMENT

In evaluating the results obtained from conservative treatment one must consider the degree of pelvic comfort obtained, whether normal menstruation was continued, and in the cases of those who were married and desired pregnancy, whether this function was improved. When conservative measures were carried out, it is to be inferred that the disease was not extensive and that the patient probably sought treatment for dysmenorrhea or to inquire about sterility.

In order to alleviate the dysmenorrhea, we have in addition to local excision been performing presacral resection. This latter was carried out in 13 of the cases in which local excision was performed. In 5 cases in which unilateral oophorectomy, and in one case in which bilateral salpingectomy was performed, a presacral resection was also carried out. We were able to trace 13 of these patients (Table IX).

TABLE IX. RESULTS: 162 PATIENTS TREATED CONSERVATIVELY

	TREATED	TRACED	IMPROVED, GRADE 1-2	IMPROVED, GRADE 3-4	UNIMPROVED	SUBSEQUENT PREGNANCY	SUBSEQUENT OPERATION	SUBSEQUENT RADIUM R	SUBSEQUENT X-RAY R	DEATHS
With presacral resection	19	13	3	6	3	4				
Without presacral resection	143	85	16	48	20	3	4*	1	2	1
Total	162	98	19	54	23	7	4	1	2	1

*Freeing of adhesions and oophorectomy in 1 case; panhysterectomy in 3 cases.

The amount of relief from pain obtained by 3 of them was Graded 1 to 2, on the basis of 4, and by 6 was Graded 3 to 4; three patients were not improved. Four, or 21 per cent of those who underwent presacral resection, however, became pregnant subsequently. This may indicate that pain, if not relieved, militates against pregnancy. This number of cases is too small, however, to draw any definite conclusions. With regard to pain, approximately 70 per cent of the patients received sufficient relief, so that it was not necessary to subject them to subsequent treatment.

In the remaining 143 cases of this group of 162, presacral resection was not performed. Eighty-five of these patients were traced. Sixteen obtained moderate improvement (Grade 1 to 2), whereas 48 obtained practically complete relief from pain (Grade 3 to 4). Approximately 75 per cent, therefore, were relieved of the pain for which they sought treatment. Twenty patients in this group were unimproved. In 7 of the cases it was necessary to apply subsequent treatment; in one case secondary oophorectomy and freeing of adhesions were carried out, and in 3 cases panhysterectomy was performed. Ovarian function was terminated by the use of radium in one case, and in two cases in which secondary pelvic inflammatory infection was suspected roentgen therapy was employed. One patient of the series died of peritonitis secondary to partial resection of an endometrial growth constricting the sigmoid. It is interesting to note that all the patients whom it was necessary to treat subsequently by irradiation or surgery were in this group in which presacral resection was not carried out. This in a way substantiates our belief that presacral resection may be of considerable value in preventing later surgical treatment even though lesions may recur.

It is not possible to show that conservative procedures for sterility are of much value since only 7 of the 55 patients whom one could reasonably expect to become pregnant did subsequently become so. However, these 7 pregnancies resulted in 10 living children. It seems to us that pregnancy can be expected only in those cases in which the disease is limited to one adnexa or to a relatively few implants which can be excised, such as we encountered in the group of cases in which presacral resection was performed.

The majority of patients who underwent presacral resection menstruated in small amounts within the first few days following operation even though it was not the regular time for menstruation. What produces this uterine bleeding is not clearly understood, but we rather suspect that it accompanies profound relaxation of the myometrium and is not due to any effect on the ovary. Menstruation in these cases remained normal, with regard to periodicity, duration, and amount of flow, as it has also in all of the other cases in which patients were treated conservatively without presacral resection. It would appear that normal menstrual function can therefore be reasonably expected in cases of limited extension of this disease, although the reproductive function may be faulty.

SUMMARY AND CONCLUSIONS

Endometriosis is an extremely important disease of young women, and its most predominant symptom is dysmenorrhea of an acquired or progressive type. Vesical and rectal pain superimposed on dysmenorrhea is almost always diagnostic. Diffuse pelvic soreness, brought about by walking or jarring of the pelvis in any way, is also suggestive.

In the majority of cases, endometriosis and its associated lesions of the uterus and adnexa will require radical surgical treatment. Radical treatment was carried out in 79.3 per cent of the present series of 884 cases.

Cases in which conservative procedures are to be carried out must be very carefully selected if recurring lesions and subsequent treatment are to be avoided. The percentage of recurrences will be reduced by limiting conservative treatment to those in which relatively few surgical

procedures will be required to remove the disease. I believe it is safer to err on the side of radicalism than to attempt preservation of ovarian function in those cases in which there is some involvement of both adnexa or in which there is considerable involvement of one adnexa and the adjacent uterine wall.

Conservative procedures cannot be recommended for the elimination of sterility, although they should be carried out whenever possible in the hope that fertility may be restored during the reproductive period of life.

Attempts to relieve dysmenorrhea by resection of the presacral nerves would seem to be definitely indicated as an adjunct to conservative surgical treatment in the hope that distress from later recurrences may be greatly minimized. Such relief of menstrual pain may also have some effect on the restoration of fertility, although with the evidence at hand presacral resection cannot be advocated as a method of restoring this function.

REFERENCES

- (1) *Blair-Bell, Wm.*: J. Obst. & Gynaec. Brit. Emp. **29**: 443, 1922. (2) *Cattell, R. B.*: New England J. M. **214**: 341, 1936. (3) *Donald, Archibald*: J. Obst. & Gynaec. Brit. Emp. **29**: 447, 1922. (4) *Graves, W. P.*: AM. J. OBST. & GYNEC. **13**: 728, 1927. (5) *Keene, F. E., and Kimbrough, R. A., Jr.*: J. A. M. A. **95**: 1164, 1930. (6) *Masson, J. C.*: Ann. Surg. **102**: 819, 1935. (7) *Pemberton, F. A.*: New England J. M. **217**: 1, 1937. (8) *Read, C. D., and Rogues, Frederick*: Proc. Roy. Soc. Med. Part 2, **22**: 1441, 1929. (9) *Sampson, J. A.*: Arch. Surg. **3**: 245, 1921. (10) *Sampson, J. A.*: AM. J. OBST. & GYNEC. **4**: 451, 1922. (11) *Smith, G. V.*: AM. J. OBST. & GYNEC. **17**: 806, 1929. (12) *Wharton, L. R.*: South. M. J. **22**: 267, 1929.

DISCUSSION

DR. FRANK A. PEMBERTON, BOSTON, MASS.—At the Free Hospital for Women we have had 470 cases of endometriosis up to 1936 proved by pathologic examination. Thirty per cent had conservative operations as against 18 per cent in Dr. Counseller's series, but in the last 100 cases there were only 12 conservative operations. There was only one death from embolism in our series which is interesting because many of the operations are difficult on account of the tough adhesions.

As regards the principal sites of the disease, both ovaries were concerned in 158, the left ovary in 133, and the right ovary in 89. The ovaries were not involved in 13 per cent of the cases, a fact which has been reported before but is not generally realized.

Of the patients treated by conservative operation, we could not follow 31. Eighty per cent required no further treatment. Further treatment of the remaining 20 per cent consisted of conservative operations in two cases, radical operation in 16, radium in 1. The x-ray has a decided place when conservative treatment fails, for with it the tumors will disappear.

Of the 83 patients who were under forty and were married 16 became pregnant once after the operation; one became pregnant twice. An interesting point is that of these 16 only 3 have needed radical operation since the pregnancy. Most of the pregnancies occurred within the first two years, so that it appears that if these patients do not become pregnant within that time they are not likely to do so. This is perhaps one reason for not doing conservative operations, for there is little point in doing an operation so that the patient may have just one more child if she already has some.

Nearly 6 per cent of these patients showed associated proliferating tumors of the ovaries. Seven of these were malignant.

There were only 14 with the rectosigmoid or vaginal septum affected. Only one of these needed treatment, a colostomy being done. She also had a hysterectomy with removal of the ovaries, and in six months the tumor in the intestine had atrophied, the bowels moved normally, and the colostomy closed.

DR. RAYMOND E. WATKINS, PORTLAND, ORE.—Early recognition of this disease seems to us of considerable importance. From the observations we have made of 15 patients with early ectopic endometriosis, 14 have had poorly developed retrocessed uteri. It was also noticed that where these early growths had occurred the body of the uterus was sharply flexed on the cervix either forward or backward. We believe that varying amounts of retrograde menstruation frequently occur in the presence of such uteri, the quantity depending on the amount of obstruction offered by the flexion in the cervix and the degree of patency of the Fallopian tube. The probable chemical irritation of the cul-de-sac is caused by such menstrual fluid.

This patient with retrodisplacement was operated upon on the third day of her menstruation. The menstrual fluid was present in her cul-de-sac and the filmy adhesions had occurred, denoting a low grade inflammatory condition. There was no history or evidence of previous pelvic infective inflammatory disease in this patient. The contents of the cul-de-sac were aspirated (20 c.c.), later centrifuged and microscopic sections showed a strip of endometrial cells which had escaped into the cul-de-sac. However, no gross evidence of endometriosis was found in this case. Such a chronic inflammatory process as seemingly produced by the monthly escape of menstrual fluid in this patient would seem to prepare the field for the reception of either transplants of cells or invite metaplasia. Dr. Sampson found such retrograde flow and cells in the cul-de-sac.

When the lesions are small and few in number, they may be excised, but frequently the patches are too scattered for excision. In such instances we have used the small cervical type of cautery to destroy them. In addition to the destruction of such early lesions, surgical replacement of the uterus would seem advisable in all cases. Following this type of therapy we have had satisfactory operative results in the majority of instances, our patients being relieved of the pain and discomfort from which they suffered before.

In the group of 15 patients referred to, the average age was 25. All had dysmenorrhea becoming progressively worse. Five of 9 married women complained of dyspareunia, stating that pain occurred in the upper vagina. Ten had associated sacral backache at menstrual time. Six had rectal pain at menstrual time. Fourteen of the 15 had retrodisplaced uteri. Twelve had unusual tenderness of the cul-de-sac on vaginal examination. Seven showed a nodular or beady condition of the uterosacral ligaments on rectovaginal examination.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—I was interested in the distribution of the lesions in Dr. Counsellor's series and noticed that there were none outside of the pelvis. Also there was only one lesion of the appendix, none of the abdominal scar. In a very much smaller series we have had three lesions in the abdominal scar and seven in the appendix.

This brings up the question of distant lesions of endometriosis. In the recent German literature there are two cases described, one of endometriosis on the anterior aspect of the thigh and another in the forearm. The only way that I can possibly conceive of these occurring is that they must get there through the arterial system. Sampson has shown that endometrial fragments are seen very frequently in the veins of the broad ligaments, but he has not described them in vessels outside.

We had an interesting experience in St. Louis with two cases. One woman had a definite inguinal gland endometriosis and a lung tumor which bled at each menstrual period. X-ray showed this tumor. No biopsy of course could be obtained. The ovaries were x-rayed and since that time she has had no more bleeding from the lungs. In a similar case a lung tumor was x-rayed, but biopsy failed to reveal anything.

We are not sure about these cases, of course, but it is suggested that they may be endometriosis of the lung. It was discussed whether such a growth could take place in the lung and the surgeons whom we consulted felt that such a thing was not possible. I pointed out that Allen had previously demonstrated the growth of endometrial tissue in the anterior chamber of the eye, and I felt that there was no reason why it could not grow in the lung. I suggested to my associate, Dr. Hobbs, that he take some rabbits, give them theelol and remove the uterus, make a return emulsion of the endometrium and inject it in the rabbits' ear veins. This was done in ten animals, the animals sacrificed in eight weeks, and we believe endometrial proliferation has been demonstrated. I think those who are working with lung tumors should keep this in mind. The work of Dr. Hobbs will be published shortly.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—I should like to ask Dr. Counsellor whether he has observed any spontaneous disappearance of massive endometriosis following conservative operations? We have had five cases, in which as much as possible of the mass was removed without destruction of the ovary, and presacral sympathectomy and ovarian neurotomy were performed. In all but one there was a complete subsequent disappearance of the masses. In the one exception there is still a small nodule in the right uterosacral ligament.

We should follow these patients as closely as we do our carcinoma patients, particularly those who have had presacral resection. We have found in a small series that operative castration gives the best results, radium treatment next, and x-ray therapy last.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I take a conservative attitude toward these cases, often going to an elaborate dissection in order to preserve ovarian function, feeling that in the event of failure the x-ray is always at hand to prevent a second operation. Frequently, multiple small areas can be well attended to by the use of the nasal cautery where dissection with the knife would be difficult. We should keep in mind always the factors of etiology in the treatment of these cases. Constrictions of the cervix should be done away with and retrodisplacements should be corrected.

A NEW, NONIRRITATING OPAQUE MEDIUM FOR UTEROSALPINGOGRAPHY*

PAUL TITUS, M.D., R. E. TAFEL, M.D., R. H. McCLELLAN, M.D.,
AND F. C. MESSER, B.S., PITTSBURGH, PA.

(From the Department of Obstetrics and Gynecology, and the John C. Oliver Memorial Research Foundation, St. Margaret Memorial Hospital)

THE injection of an opaque medium into the uterus and Fallopian tubes for the purpose of x-ray visualization, suggested by Cary¹ and independently by Rubin² in 1914, is with certain limitations a valuable diagnostic procedure.

In sterility studies in our clinic this procedure has been used only as an adjunct to the Rubin insufflation with carbon dioxide gas. This latter test is entirely sufficient to demonstrate patency of the tubes, is safer and simpler, and also is considerably less expensive for the patient than x-ray examinations. We resort to uterosalpingography only when tubal obstruction is demonstrated by the Rubin test, or when small tumors or polyps of the uterus are suspected.

Proper technic of injection of an opaque medium will usually locate fairly accurately the site of a tubal obstruction, or the presence of small new growths. By proper technic, we refer to the method recommended by Hyams³ which consists in the injection of fractional doses of 2 c.c. each of the medium, an x-ray film being exposed after each such dose until a series of five pictures have been made, or fewer if the patient complains unduly of pain. The maximum capacity of the uterus and tubes is about 10 c.c., and more than this may be harmful, especially if obstruction exists. This fractional or serial method has many diagnostic advantages over that of a single large injection with only one or at the most two x-ray pictures.

Even with this careful technic, which effectually prevents overdistention of these cavities, and even with the limitation of uterosalpingography to cases in which it is clearly indicated, untoward reactions occur all too frequently. We have had several instances of acute "chemical" salpingitis, parametritic masses, and occasional allergic reactions following the use of iodine in oil. The liberation of free iodine from these solutions has been thought by us to be the cause of some of these reactions. Late or delayed reactions are probably due to the foreign body effect of oil on the peritoneum, and many instances of encysted oil in the peritoneal cavity have been reported in the literature. The persistent presence of iodized oil can be demonstrated by x-ray examination days or weeks after its injection.

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

As a result of these unfortunate experiences, we undertook to develop a medium which would be nonirritating and also quickly resorbed and excreted. A preliminary report of our work was published in 1937.⁴

Mono-iodomethane sulphonate of sodium (skioldan) is an organic compound containing 52 per cent of iodine in stable combination. In aqueous solution it has been used extensively by urologists. Its injection intravenously for excretion urography and its direct injection

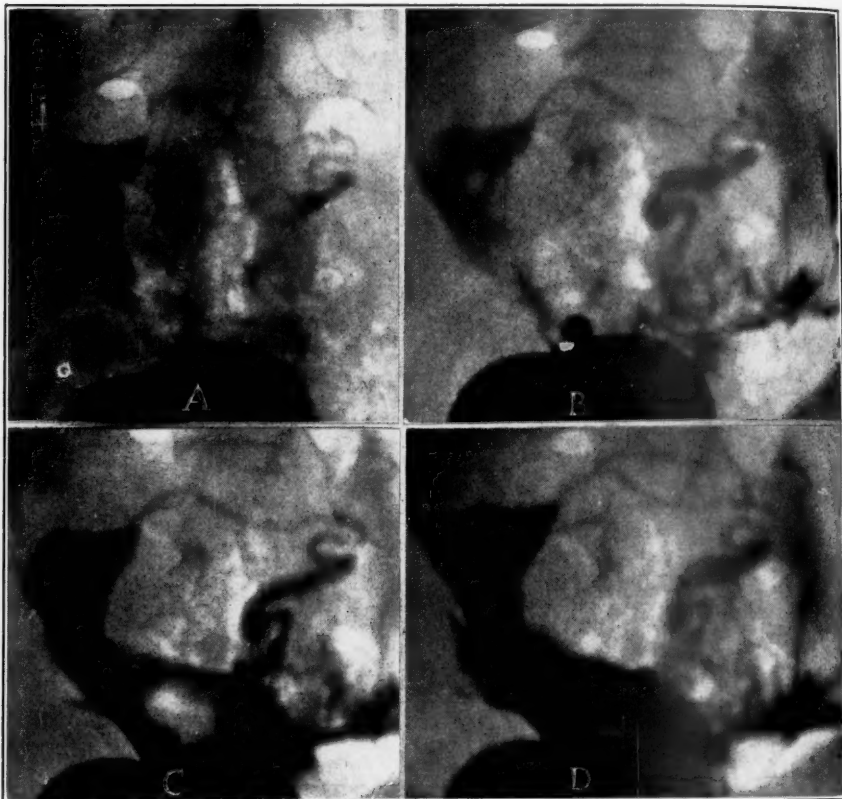


Fig. 1.—Serial uterosalpingograms (Hyams' technic) using 2, 4, 6, and 8 c.c., respectively, of skioldan-acacia solution. A and B show filling defects in uterine cavity due to polyps, not visible in C and D, being obscured by further distention. Left tube is patent, and right tube occluded with displacement of uterus toward right (probably adhesions).

into the urinary passages for retrograde pyelography show it to be free from local irritative or generalized reactions, and in other instances direct injection into the arteries for arteriography has not been attended by untoward effects. In experimental animals after the injection of large amounts of this preparation no free iodine or inorganic iodine could be detected in the blood or urine, so that iodism may be considered as virtually impossible following its use. Moreover it is rapidly excreted. When injected intravenously into rabbits,

the rate of excretion is approximately 47 per cent in one hour, 76 per cent in three hours, and 89 per cent in nine hours. The rate of excretion in man (normal kidneys) is even faster.

We found that the aqueous solution of this substance was unsuitable for uterosalpingography because of its lack of viscosity. Even a small amount of the watery solution spurted through the uterine cavity and the tubes because it was so fluid. As a result of this these x-ray pictures were uniformly unsatisfactory. Consequently an attempt was made to thicken the preparation so that its chemical con-

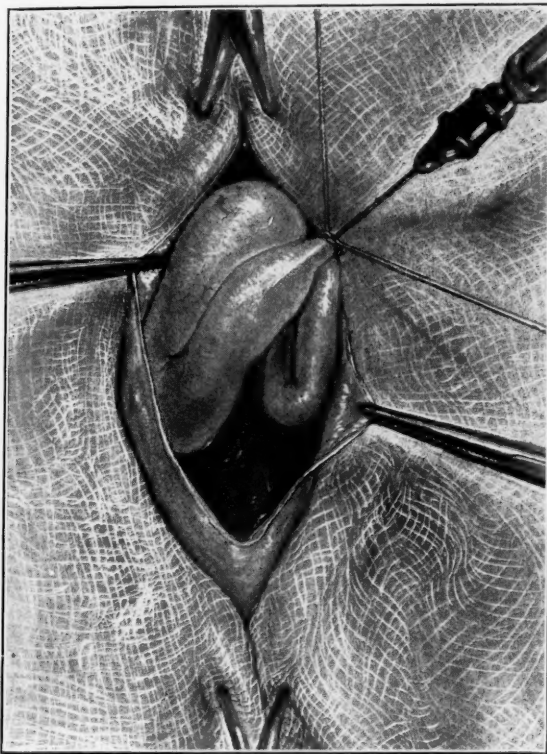


Fig. 2.—Technic of direct injection into one horn of rabbit uterus. The lower portion is ligated to prevent leakage through cervix, and opposite horn is used as normal control during subsequent histologic search for evidence of inflammatory or irritative reaction.

tent would remain the same as that already found suitable for x-ray visualization in urologic work, while its viscosity would be approximately the same as that of the more familiar iodized oil.

It is not necessary to recount here the details of the tedious and sometimes discouraging series of preparations made and discarded. Glucose, propylene glycol, starch, tragacanth, and other similar thickening mediums were tried and by animal experimentation found unsatisfactory. Dr. O. W. Barlow of the Winthrop Chemical Company's Research Laboratory suggested and prepared a mixture of the mono-

iodomethane sulphonate of sodium (40 per cent) with acacia (20 per cent) which finally solved this problem admirably.

The suggestion has been made that because acacia solution injected intravenously in copious amounts has proved dangerous in some in-



Fig. 3.—Rate of resorption shown by x-ray. *A*, Shows ligated horn of rabbit uterus thirteen minutes after injection with skiodan-acacia; *B*, shows same rabbit ninety-three minutes after injection, shadow now appearing in urinary bladder as skiodan-acacia is taken up from tube and is being excreted in urine.

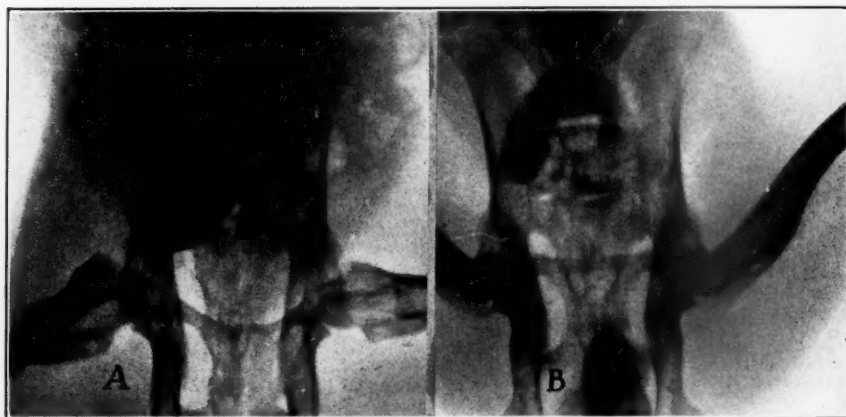


Fig. 4.—Similar to Fig. 3. Another rabbit, *A*, showing uterine shadow immediately after injection; *B*, showing fading of uterine shadow and formation of bladder shadow thirty-five minutes after injection.

stances, its intrauterine use might be similarly undesirable. It must be remembered however that only 10 c.c. are injected, and these into the uterus, not into a vein. If a blood vessel were invaded accidentally the amount received into the circulation would be so small that it could not, conceivably, cause harm.

We have carried out extensive experimental investigations in the Oliver Research Laboratory at our Hospital to determine any possible harmful and irritative effects of this new preparation, and independently, similar and elaborate studies have been made by Dr. Barlow in the Winthrop Research Laboratories. After satisfying ourselves that such effects were lacking in animals we began its clinical use in the hospital.

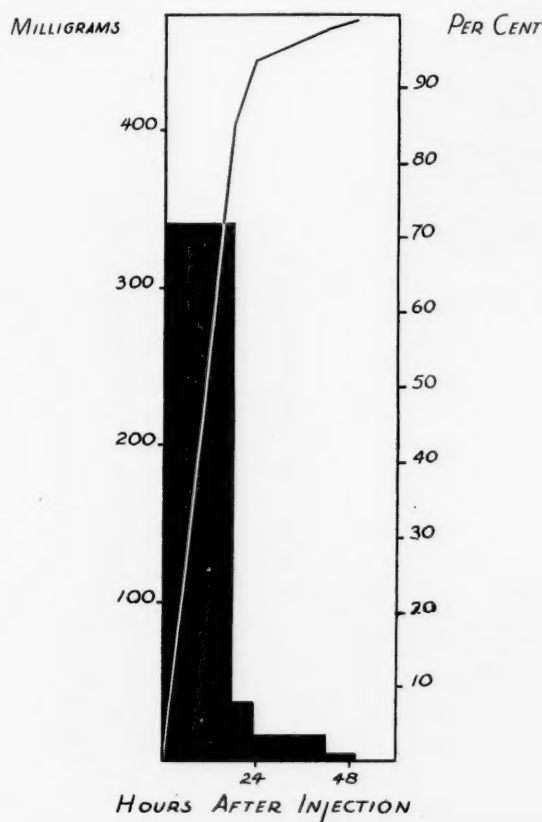


Fig. 5.—Rate of elimination shown by chemical analysis. Skiodan-acacia (400 mg.) injected into doubly ligated uterine horn. Vertical bars indicate milligrams of iodine compound in urine; line, total elimination, percentage of amount injected.

SUMMARY OF EXPERIMENTS

Our preliminary experiments fall into three parts: First, an attempt to determine any local inflammatory effect from the introduction of the radiopaque compound into the female genitalia or peritoneum of rabbits; second, a study of the resorption of the compound after its injection into the uterus, and its excretion by the kidneys as shown by x-ray films; and third, the study of the speed of resorption and elimination by the kidneys, by means of chemical analyses.

1. *Local Irritative Effects.*—The female rabbit exhibits the extremest manifestation of bifid uterus, possessing two separate and complete uteri, each with its individual cervix in the vault of the vagina. This permits the isolation of a substance introduced into one of the uterine horns, preserving the other for control.

Rabbits were treated by injecting 1 c.c. quantities of sterile skiodan-acacia into one intact horn of the uterus. A curved metallic catheter was inserted through the vestibulum so that its tip was well up into the vagina. A ureteral catheter, threaded through the metallic one, was guided past one of the cervixes of the double uterus into the lumen of the uterine horn by careful manipulation of the intact genitalia through an abdominal incision. The skiodan-acacia was injected through the fine catheter by means of an attached syringe. The catheters were then withdrawn and the incision closed.

These rabbits were examined by biopsy forty-eight hours to so long as seventy-nine days after injection. The gross condition of the genitalia and peritoneum was noted, and specimens of both uterine horns removed for microscopic examination.

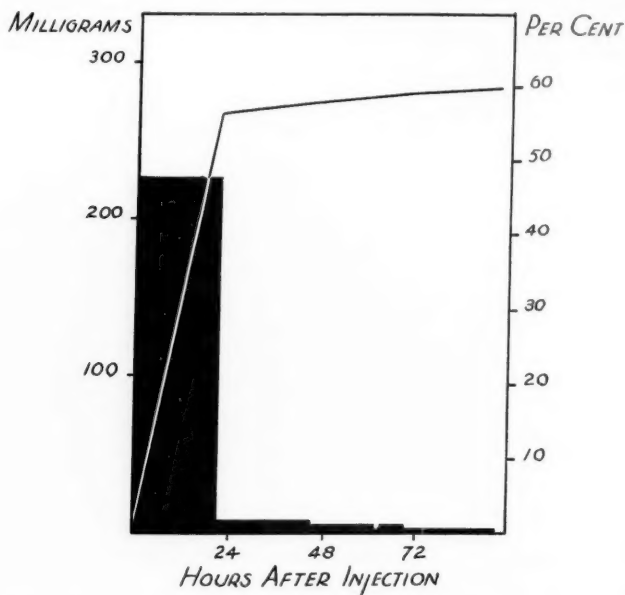


Fig. 6.—Skiodan-acacia (400 mg.) injected directly into peritoneal cavity (compare with Fig. 5).

No more pathologic change could be observed on gross or microscopic examination than would be expected from the forcible distention to which the uterus was subjected.

The effect of skiodan-acacia on the Fallopian tubes of rabbits was next studied.

The uterus was exposed by a low midline incision, and a hypodermic needle inserted distally through the wall and into the lumen of one uterine horn. A ligature was passed around the horn and needle. After injection of the predetermined amount of fluid, the ligature was tightened as the needle was withdrawn so that the fluid could not pass into the vagina, or into the peritoneal cavity through the needle puncture.

At the end of forty-eight to seventy-two hours, biopsies were performed, and specimens from the uteri and tubes fixed for microscopic examination. In spite of the fact that the treated uterine horns were found uniformly to be distended with fluid on biopsy, no more evidence of specific irritant effect on the uteri could be observed than could be accounted for by mechanical distention. No microscopic difference was seen between the treated and untreated Fallopian tubes.

2. *Rate of Resorption as Shown by X-ray.*—X-ray films were taken of rabbits in which one horn of the uterus had been injected with 1 c.c. of skiodan-acacia, and ligated near the cervix. Various time intervals following injection were chosen, to study the rate at which the shadow of the injected horn disappeared, and at which a shadow appeared in the bladder due to absorbed and excreted skiodan.

The shadow of the uterus, at first sharp and clear, became faint toward the end of an hour; in some cases it disappeared completely within one or two hours. In only one instance was the shadow of a Fallopian tube identified. It is probable that the rabbits' tubes, being of small caliber, do not contain enough of the radiopaque material to cast a shadow except when they are unusually well developed.

Coincidentally with the fading of the uterine shadow, sufficient skiodan is absorbed and excreted into the urine to cast an increasingly distinct shadow of the bladder. This shadow is first seen, under our experimental conditions, about thirty-five to forty minutes after the uterus has been injected.

Dr. Barlow reports that experiments on albino rats show that the incidence of positive abdominal films is 100 per cent within five minutes after injection, 80 per cent within ten minutes, 40 per cent within fifteen minutes and only 30 per cent within twenty minutes. Clinical observations confirm these findings.

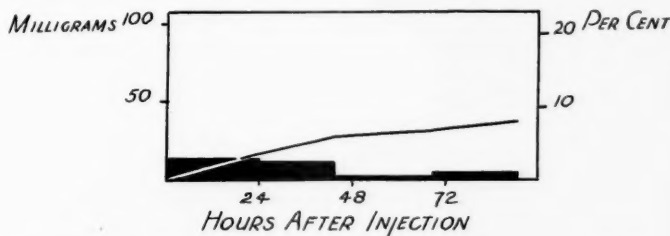


Fig. 7.—Iodized oil (600 mg.) injected directly into peritoneal cavity. Compare with Figs. 5 and 6, noting relative slowness and incompleteness of resorption and excretion. (Note: Vertical scale is twice that of Figs. 5 and 6.)

3. *Excretion of Compound in the Urine.*—Rabbits were given injections of skiodan-acacia, and their total output of urine collected at one- to three-day intervals. Iodine was determined on aliquots of these specimens using a modification of Kendall's method.

One cubic centimeter of skiodan-acacia was injected into the right uterine horn of rabbits, and the uteri ligated proximally. The excretion of the iodine compound in their urine was then studied. The greater part of the iodine compound administered was excreted at the end of the first eighteen hours, after which the rate fell off sharply. Substantially all of the injected skiodan had been accounted for by the end of the third day after injection.

Since these experiments gave no clue to the site from which the compound was absorbed, two further experiments were carried out. In the first, 1 c.c. of skiodan-acacia was injected directly into the lumen of one uterine horn of the rabbit, and ligatures tied proximally and distally to the site of the injection, the distal ligature including about one-half of the length of the tube. Animals were placed in metabolism cages, and their output of urine analyzed at intervals for iodine compound as in the previous experiment. The rate of absorption of skiodan through the intact uterus and tube is distinctly lower than from the peritoneum. For comparison, the rate of absorption of iodized oil, and the excretion of its iodine in the urine, were studied by methods similar to those used in the previous experiments. Excretion was found to occur at a markedly lower rate, but it is impossible to compare this rate with that at which skiodan was excreted, since, in rabbits receiving iodized oil, the urinary output decreased profoundly. The rate of iodine excretion increased slightly as the daily volume of urine again approached normal.

From the experiments on urinary excretion as well as from the x-ray studies, it is apparent that skiodan is rapidly absorbed from the uterus, and from the peritoneum, and the greater part excreted by the kidneys within eighteen hours. Whether or not iodized oil could be eliminated as readily from the rabbit's body, if anuria did not follow its administration, cannot be definitely decided from our experience. It seems unlikely, considering the lipoid nature of the material.

CLINICAL APPLICATION

Our clinical results from the use of this nonirritating radiopaque substance have been uniformly satisfactory. In a fairly large series of patients there have been no evidences of inflammatory reactions, either immediate or delayed. Moreover, the x-ray pictures seem sharper and clearer than with the iodized oil preparations.

X-ray pictures taken within a few hours after the original clinical diagnostic series show that the radiopaque substance has entirely disappeared.

Further investigations are being undertaken in our Research Laboratory to determine the actual rate of excretion of the compound through the urine of these patients. Another study is being projected to determine the ultimate fate of the acacia thus injected. This appears to be excreted through the bowels.

SUMMARY

1. Uterosalingography, as an adjunct to transuterine tubal insufflation in sterility studies, is a useful diagnostic measure in a certain restricted group of case instances.

2. Iodized oil injected into the uterine cavity and the Fallopian tubes as the opaque medium for x-ray visualization is followed too frequently by sharp reactions, either from chemical irritation by the iodine, or allergic in type as though from the oils.

The foreign-body effects of iodized oil, persisting as this substance does for indefinite periods of time after injection into the abdominal cavity, result often in encysted masses with local acute and chronic peritonitis.

3. In an effort to avoid such reactions, a new nonirritating radiopaque compound has been devised, consisting of mono-iodomethane sulphonate of sodium (skiodan) (40 per cent) with acacia (20 per cent).

4. This chemical compound does not release free iodine and is rapidly excreted from the body through the urine. The acacia, added for viscosity, does not have a foreign body effect as do poppy seed or sesame oils.

5. Adequate animal experiments were conducted to demonstrate, histologically and chemically, the correctness of the foregoing statements before beginning the clinical use of this medium with patients.

6. It has now been used in our clinic in a series of patients over a period of nearly two years without clinical evidence of inflammatory or other reactions, either immediate or delayed. Moreover, the x-ray pictures appear to be more distinct than with the iodized oil preparations.

7. Further studies are now being made by us to determine the rate of excretion of mono-iodomethane sulphonate of sodium through the urine, and also the fate of acacia injected into body cavities.

It is suggested that this preparation may be of distinct use in bronchoscopic work. Our Research Laboratory is now collaborating with the Department of Neuro-surgery at this Hospital in an effort to develop a modification of this preparation suitable for intraspinal and intracranial use.

We are indebted to the Winthrop Chemical Company for a generous quantity of supplies used in these studies, and to Dr. O. W. Barlow of their Research Laboratories for his active cooperation and helpful suggestions.

REFERENCES

- (1) *Cary, W. H.*: Am. J. Obst. & Dis. Women & Child. 69: 462, 1914. (2) *Rubin, I. C.*: Zentralbl. f. Gynäk. 38: 658, 1914. (3) *Hyams, M. N.*: Surg. Gynec. Obst. 60: 224, 1935. (4) *Titus, P., Tafel, R. E., McClellan, R. H., and Messer, F. C.*: AM. J. OBST. & GYN. 33: 164, 1937.

DISCUSSION

DR. ALEXANDER M. CAMPBELL, GRAND RAPIDS, MICH.—When in the field of gynecology a comparatively new diagnostic procedure is suggested, which involves the entrance of a foreign substance into the inner genitalia, which nature has guarded with certain defense barriers, the physician who assumes the responsibility of making such a test should make the following inquiries:

1. What is the danger attending such a procedure?
2. How much pain and disability will this measure cost the patient?
3. Has the test been done in a sufficient number of cases, and with such a satisfactory technic that conclusions of value may be drawn from it?
4. What information can be obtained that cannot be gained by a careful gynecologic examination, made under anesthesia if necessary?
5. Can its field of usefulness be extended toward more precise diagnosis in gynecology?

After an experience of fifteen years in which we have used lipiodol in uterosalpingography we have never observed the clinical evidences of infection or other reactions referred to by Dr. Titus, and reported by others. We have attributed this to the fact that we have used this in selected cases, in our sterility studies, in private practice, and have been extremely careful and gentle in our technic.

As our experience increased, however, we observed that for intrauterine diagnosis lipiodol has definite limitations. We have, therefore, searched for a more satisfactory medium, and were much interested in the reports of Guttman and Stahler, who in 1933 used as a medium thorium dioxide solution for uterine and tubal shadow demonstrations. They warned of its irritating qualities and after using it a few times we discontinued it for that reason. Soon after this my associates attempted to develop a more satisfactory medium and succeeded by using a colloidal suspension of thorium hydroxide. This preparation is known as thorad and is injected into the uterus by the open method. It adheres to the mucous membrane and gives satisfactory demonstration of the relief of the endometrium. We use this preparation routinely in an attempt to diagnosticate minute intrauterine lesions, such as early carcinoma, polyps, and small fibroids where no pathology can be demonstrated by the ordinary careful gynecologic examination. In the investigation of uterine bleeding it is of value. When lesions are diagnosed by this method, it is a guide to the placement of radium when radium is used in the uterus. In our experience it has been a most valuable diagnostic aid.

We have had no personal experience with skioldan in the human female genital tract. Dr. Titus sent us some ampoules of it a few weeks ago, and we injected

5 c.c. of this preparation into the genital tract of a rabbit, and at the same time injected the same amount of lipiodol into a rabbit of equal size, with a view of comparing the value of these media.

The films indicate that lipiodol is more radiopaque than the skiodan but that it shows less detail. The rabbit that received the skiodan apparently suffered no discomfort following its introduction, while the rabbit that received the lipiodol had definite abdominal cramps.

An autopsy a few days afterward in both rabbits showed no changes in the uterus and tubes of the rabbit that received the skiodan, while definite congestion was demonstrated in the rabbit injected with lipiodol.

Dr. Titus' presentation marks an evolution in the use of radiopaque media in gynecology, and we will give it a trial and compare it with our fifteen years of experience in the use of lipiodol and our shorter experience with thorad in the hope that it will supersede these media in diagnostic precision in the field of gynecology.

DR. JOSEPH L. BAER, CHICAGO, ILL.—At the Michael Reese Hospital we have had to date no untoward results from lipiodol. It has the advantage also of remaining in situ and allowing the genitalia to be studied. We have not had the inflammatory end results and difficulties which Dr. Titus describes, and therefore thus far have been quite content to go on with the use of lipiodol, which of course remains over long periods of time but which is apparently innocuous in the human being.

DR. TITUS (closing).—Those of us who have not had difficulty with the use of iodized oils have been extremely fortunate. I have had three very distinct and definite reactions, one a sharp one where the patient proved afterward to be sensitive to iodine. Another developed a parametritic mass, evidently an arousing of an old and unsuspected infection.

The rapid resorption and disappearance of the skiodan are distinct advantages in view of the fact that there have been a number of reports in the literature of encysted masses of oil, with evidences of localized peritonitis, found at laparotomy even a long time after treatment of this sort.

I can confirm Dr. Campbell's experimental findings, as ours were similar to his in that the x-ray shadows seemed sharper with this medium than with iodized oil.

The preparation was made up as a concentrated aqueous solution of skiodan, and then diluted down with acacia in solution so that the mixture finally contained 40 per cent of skiodan and 20 per cent of acacia, the balance being water. Acacia is added for viscosity, as explained in the paper, the mixture being approximately the same in this respect as ordinary iodized oil.

COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA*

MANAGEMENT AND END RESULTS

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., BOSTON, MASS.

LACERATION of the perineum involving the anal sphincter and rectovaginal septum has always been looked upon as one of the most discouraging conditions affecting woman. In a previous publication, I¹ reported the end results of 42 cases. Since then, during a period of nearly ten years, I have operated upon 50 more patients, a total of 92 operations in a period of approximately twenty-two years, or about 4 a year. Improvement in obstetric practice has been responsible for a diminution of this disorder during the last decade. Several of my patients had carried the affliction for a number of years, one of them 27, and another 50 years. A great many had occurred before episiotomy was resorted to as frequently as it is today. Ten of the women in the series had had an unsuccessful primary repair and presented themselves with complete separation of the sphincter ends, a large rectovaginal fistula and a bridge of perineal tissue which had held between the two. A rectovaginal fistula may occur during the process of healing by the infection of some of the stitches. Most of the small ones heal spontaneously after the catgut knot is absorbed or discharged, while others need a subsequent closure. In 9 patients I sutured the tear shortly after childbirth and in 83 the repair was accomplished as a gynecologic operation. These 92 patients were obtained from a wide geographic area and represented an occasional complete laceration in a given district. A third degree tear of the perineum, with its not infrequent accompanying rectovaginal fistula, may be avoided in practically all instances by resorting to an episiotomy. The manual dilatation of the perineum advocated by some obstetricians may decrease the incidence of this disorder but does not give the protection obtained by a properly performed incision. Furthermore, with manual dilatation the separation of the levator ani muscles under the intact mucous membrane and skin may occur with a resultant rectocele, a condition but seldom encountered after well-sutured perineal incisions. An episiotomy may be median or mediolateral. The protagonists of the mediolateral object to the median incision or perineotomy on the principle that if the median incision is extended by the advancing presenting part it may go through the sphincter ani muscle. This complication may be prevented by continuing the incision so that it encircles the anus on one side, thus avoiding injury to the sphincter. It has been my custom to use a

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, North Carolina, May 30, to June 1, 1938.

median incision when a moderate amount of room was required and a mediolateral when the opposite obtained. The lateral incision is best made on the side of the presenting part, in other words, a right episiotomy in a right position and a left episiotomy in a left position. Occasionally it may be advantageous to incise the two sides.

In a primary repair, emphasis must be placed on layer sutures and approximation without tension. Mass suturing often leads to a rigid, scarred, sensitive pelvic floor. Sutures which are set snugly at the time of repair will be found to be cutting through the tissues in twenty-four hours, when the edema has set in and, conversely, sutures which appear to be loose at the intervention will be set properly the next day. The puerperium is shortened rather than prolonged and involution occurs faster if the repair is done soon after delivery, but, if the parturient is not seen shortly after labor, a minimum of three months are allowed to elapse before operating. Involution has then taken place, the edema has disappeared, scar tissue has formed between the torn edges and, in my experience, better operative results are obtained than when a so-called intermediate operation is attempted about ten days after labor.

PREOPERATIVE PREPARATION

The patient is prepared by thoroughly emptying the bowel by means of castor oil, administered four days and two days before operation. She is given a cleansing enema, preferably saline, the afternoon before, but none the morning of operation, and, for the two preceding days her diet is one that contains but little residue. Under anesthesia the operative field is prepared by gently scrubbing the external genitals and the vagina with tincture of green soap and warm sterile water, using gauze at the end of a sponge stick. The parts are then irrigated with a solution of potassium mercuric iodide, 1 to 1,000, strong antiseptics not being used.

TECHNIC OF OPERATION

Two general principles are employed in the repair of a complete laceration of the perineum: (1) The flap method, advocated by Warren, (a), and modified by Ristine, (b), Farrar, (c), Miller, (d), and others. (2) The layer method of repair with or without rectal suture. I have employed the latter method with rectal suture and since my results have been satisfactory, I have not had occasion to change.

The pelvic floor is opened by a capital H-shaped incision. The lateral incision on each side extends from a point below the duct of the vulvovaginal gland to the retracted end of the sphincter. The transverse incision joins the two lateral by running through the edge of the scar tissue uniting the rectal and vaginal walls. A flap of posterior vaginal wall is raised upward exposing the rectum which is separated from the levator ani muscles by blunt dissection. The anterior rectal wall is picked up by an Allis forceps at the upper angle of the tear and put on stretch, the scar tissue is trimmed from the edges and the torn edges are united by interrupted sutures of fine prepared silk (Dermal), the knots being tied within the bowel lumen. The perirectal tissues are approximated over the first suture line by a continuous stitch of No. 0 or No. 00 chromic catgut, avoiding constriction of the tissues. The perirectal tissues are further approximated, without tension, by figure-of-eight sutures of the same material. The rectal wound is thus closed in three layers. The torn ends of the sphincter ani muscle are dissected out of their bed of scar tissue and approximated with a figure-of-eight suture of No. 1 chromic catgut. If there is tension on the sphincter ends a reinforcing suture of silkworm gut may be introduced by passing

it through the skin of one side, the sphincter muscle and the skin of the other side, to be tied at the completion of the operation. The excess of vaginal flap is resected, the edges of the vaginal incision are united with No. 1 chromic catgut interruptedly, and the levator ani muscles and their fascia are brought together by three interrupted stitches of the same catgut. The external perineum may be closed in three ways: (1) By approximating the triangular ligament with a running stitch of No. 0 or 00 tanned catgut, and the skin by a subcuticular or continuous suture of the same material; (2) by interrupted sutures of No. 0 chromic catgut, which in their course pick up the united levator ani muscles to obliterate dead space; (3) if there have been previous attempts at repair and if considerable scar tissue is present, interrupted fine silkworm gut sutures may be used to advantage in the closure. Emphasis must be placed on fine suture material and approximation without tension. As my experience with this operation has increased, I have used finer and finer catgut.*

POSTOPERATIVE CARE

Morphine sulphate and deodorized tincture of opium are administered as necessary. For the first six days the diet consists of hot and cold fluids, without residue such as beef tea, strained soup, bouillon, the white of an egg, with two ounces of strained orange juice and water to make four ounces, tea with lemon and black coffee. Milk is not allowed. The external suture line is painted with a 4 per cent solution of mercurochrome after micturition or catheterization. After forty-eight hours a short 4 per cent boric acid douche is given daily, using a soft rubber catheter as a tip. On the morning of the seventh day the patient is given a Seidlitz powder. One-half hour later six ounces of warm sweet oil are instilled into the rectum and retained. She is given a low soapsuds or saline enema when the desire to empty the bowel becomes apparent and she is instructed not to strain. After this a soft diet is allowed and by the ninth day a full diet. The silkworm gut suture or sutures, if used, are removed on the ninth day, she is allowed out of bed on the twelfth day and usually discharged on the fourteenth or fifteenth postoperative day, to be examined again one month later.

TABLE I. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Summary of Cases

Fresh complete laceration of the perineum	9
Old complete laceration of the perineum	33
Complete laceration of the perineum with involvement of anterior rectal wall	34
Complete laceration of the perineum with involvement of anterior and posterior rectal walls	1
Complete laceration of the perineum with rectovaginal fistula	10
Rectovaginal fistula	5
Total	92

TABLE II. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Etiology

1 Complete laceration, child 7 years of age, impaled on an iron picket fence.
1 Complete laceration, child 7 years of age, following rape.
1 Rectovaginal fistula following a perineotomy for vaginismus.
1 Rectovaginal fistula following an operation for fistula in ano.
88 Complete laceration and rectovaginal fistula resulting from the trauma of labor.

*For the illustrated technic of this operation the reader is referred to the AM. J. OBST. & GYN. 17: 475, 1929.

Table I summarizes the 92 cases reported in this paper. In this series one patient had been unsuccessfully operated upon twice, and seven patients once. The youngest patient was 7 years of age and the oldest 70 years. The average age was 36 years. Spinal anesthesia with a small dose of novocaine crystals was resorted to 15 times and general anesthesia 77 times.

TABLE III. ADDITIONAL LESIONS IN THE GROUP OF 83 PATIENTS WITH OLD COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Laceration of right labium majus	1
Prolapse of rectum	3
Rectal polyp	1
External thrombotic hemorrhoid	1
Rectocele	4
Cystocele	13
Vesicovaginal fistula	1
Laceration of cervix	31
Erosion of cervix	4
Cervical polyp	2
Hypertrophied cervix	2
Myoma uteri	1
Procidentia uteri	3
Second degree prolapse	3
Descensus uteri	1
Third degree retroversion	1
Second degree retroversion	2

TABLE IV. ADDITIONAL OPERATIONS IN THE GROUP OF 83 PATIENTS WITH OLD COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Repair of right labium minus	1
Moschcowitz operation for prolapse of rectum	1
Fundic hysterectomy, bilateral salpingo-oophorectomy	
Bladder advancement, fixation of uterus to abdominal wall	
Excision of rectal polyp	1
Evacuation of clot from external thrombotic hemorrhoid	1
Kelly operation for relaxed vesical sphincter	1
Resection of suburethral fold	1
Operation for cystocele	10
Dilatation and curettage	31
Cauterization of cervix	2
Conization of cervix	1
Cervical polypectomy	2
Right trachelorrhaphy	2
Bilateral trachelorrhaphy	20
Schröder amputation of cervix	2
Amputation of cervix	9
Interposition operation	5
Vaginal hysterectomy	2
Round ligament suspension of the uterus	2

NOTE.—The laparotomies for suspension of the uterus were done two weeks after the plastic repair, while the Moschcowitz operation for prolapse of the rectum and fundic hysterectomy were performed two weeks before the reconstruction of the complete tear of the perineum.

Ninety-four additional operations were performed on this group of 83 patients with complete laceration of the perineum and rectovaginal fistula, as depicted in Table IV. Two laparotomies were performed. In one patient the uterus was suspended two weeks after the plastic repair, while in another the Moschcowitz operation for prolapse of the rectum and a fundic hysterectomy were resorted to two weeks before the reconstruction of the complete tear of the perineum. For obvious reasons an abdominal operation should not be performed in conjunction with the reconstruction of a perineum lacerated in the third degree.

Table II summarizes the etiology of the 92 cases.

The case of the first child, 7 years of age, who had a complete laceration of the perineum with involvement of the rectovaginal septum as a result of having been impaled on an iron picket fence is interesting from two standpoints. If in a child of that age, reconstruction of the parts is not carried out soon after the accident,

TABLE V. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA
Postoperative Complications

Rectovaginal fistula	5
Ischiorectal abscess with rectovaginal fistula	2
Ischiorectal abscess with perineal sinus	1
Perineal sinus	1
Slight separation of sphincter ends	1
Small area of skin slough above sphincter ani	1
Hypertrophied tabs of rectal mucosa	1

Twelve patients had postoperative complications

They were treated as follows:

- Case 1. Small rectovaginal fistula, repaired ten months later, satisfactory end result.
- Case 2. Small rectovaginal fistula, repaired five months later, satisfactory end result.
- Case 3. Small area of skin slough above sphincter ani, satisfactory healing by second intention.
- Case 4. Small rectovaginal fistula, repaired seven months later, satisfactory end result.
- Case 5. Ischiorectal abscess with perineal sinus, right. Incision and drainage four months after original operation, healing satisfactory.
- Case 6. Slight separation of the sphincter ends, healing by scar tissue, good bowel control.
- Case 7. Small high rectovaginal fistula. This patient had been operated on for a large rectovaginal fistula which had followed a perineotomy for vaginismus. She was lost sight of.
- Case 8. Seventy years of age. Convalescence complicated by bronchopneumonia and coronary disease. Discharged from the hospital with a small rectovaginal fistula. She has refused to report for examination.
- Case 9. Perineal sinus, healed by second intention; satisfactory end result.
- Case 10. Ischiorectal abscess with fistula two months after operation. Excision of fistula, healing by second intention; satisfactory end result.
- Case 11. Hypertrophied tabs of rectal mucosa developing after operation. Injection of tabs with sclerosing solution; satisfactory result.
- Case 12. Small ischiorectal abscess and fistula, left, seven months after operation. Spontaneous drainage, healing by second intention; satisfactory end result.

TABLE VI. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA
End Results

80 patients, 87 per cent, had satisfactory results, that is, a good perineal body and sphincter control.

12 patients, 13 per cent, developed postoperative complications as follows:

- 6 patients had additional operative procedures and secured a satisfactory end result.
- 4 patients had mild infectious complications which healed spontaneously. All obtained satisfactory bowel control.
- 1 patient had a small rectovaginal fistula and was lost sight of.
- 1 patient had a small rectovaginal fistula and has refused to report for examination.

The final result in 90 of 92 patients, approximately 98 per cent (97.8 exact), was satisfactory.

The final result was doubtful in 2 patients with small rectovaginal fistulas when discharged from the hospital (approximately 2 per cent), as no follow-up could be obtained.

and scar tissue is allowed to form, it becomes increasingly difficult to secure a satisfactory repair. If a successful repair is not attained there is imperfect development of the lower rectum, anus, and external genitals. In this particular case it was necessary to obtain needles small enough to work with from the eye department of the hospital. Healing took place by first intention and she secured a satisfactory anus, perineum, and vagina. She was seen for some time after operation, then disappeared. Eleven years later, when she was eighteen years old, she reported to the clinic complaining of dysmenorrhea. Examination then showed perfectly developed external genitals and anus. The scar in the external perineum could not be identified. Eighty-eight of these cases followed the trauma of childbirth, the usual etiologic factor. Complete laceration of the perineum and rectovaginal fistula is frequently complicated by other lesions. Table III shows that in the 83 patients who had old lacerations and fistulas there were 74 additional lesions.

SUMMARY

1. A complete laceration of the perineum may be prevented by employing one of three methods when the indication arises: (1) perineotomy, (2) episiotomy, (3) manual dilatation of the perineum and vagina.
2. Perineotomy, or median perineal incision, is of value when the disproportion between the presenting part and the vaginal outlet is moderate.
3. Episiotomy or lateral perineal incision should be resorted to when a great deal of room is required, as in difficult forceps operations, and when the presenting part is overlarge.
4. Manual dilatation of the perineum and vagina is a satisfactory method of preparing the birth canal before version and extraction operations.
5. The technic of operation for repair of complete laceration of the perineum and rectovaginal fistula is discussed.
6. The preoperative and postoperative care are described.
7. Emphasis is placed on careful approximation of the tissues with fine suture material applied without tension.
8. Ninety-two personal cases are reported.
9. The end result was satisfactory in 90 patients, 98 per cent, 12 of whom, 13 per cent, developed postoperative complications. In two patients, approximately 2 per cent, discharged from the hospital with small rectovaginal fistulas, the final result was not ascertained.
10. A careful preoperative preparation, meticulous technic, and postoperative care, preferably under the immediate supervision of the operator, play an important role in securing satisfactory healing.

REFERENCES

- (1) Phaneuf, L. E.: *AM. J. OBST. & GYNEC.* 17: 475, 1929. (2) Warren, J. Collins: *Boston M. & S. J.* 98: 25, 1878. (3) Ristine, C. E.: *Am. J. Obst.* 41: 365, 1900. (4) Farrar, Lillian K. P.: *Surg. Gynec., Obst.* 741, 1930. (5) Miller, N. F., and Brown, W.: *AM. J. OBST. & GYNEC.* 34: 196, 1937.

DISCUSSION

DR. GEORGE GRAY WARD, NEW YORK, N. Y.—Dr. Phaneuf's tenth conclusion is, I think, the crux of the whole matter. The outstanding essential for success is minute attention to detail.

Either technic of operation, the flap or the layer method, may be successful. The type selected should be adapted to each case, although personally I prefer the flap method wherever possible.

In the postoperative treatment of these cases two methods are employed by different operators: Delayed bowel movements where the bowels are kept inactive for a period of seven days or longer, and the method of giving saline cathartics in small repeated doses early to produce liquid stools after the third or fourth day. Both of these methods may be successful, and I am inclined of late to the earlier movement of the bowels rather than tying them up for a long period.

I have had the records at the Woman's Hospital gone over for the past fifteen and twenty years and find the following data and end results:

TABLE I. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. TOTAL NUMBER OF PATIENTS OPERATED UPON (GYNECOLOGIC AND OBSTETRIC)—282

Gynecologic patients	128 (20 yr.)
Number of operators	22
Cases with previous attempts at repair prior to admission to woman's hospital	20
Obstetric patients	124 (15 yr.)
Total patients with satisfactory result	242 (96.02%)

TABLE II. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE (1918-1938). GYNECOLOGIC SERVICE

Total number of patients operated upon	128
Total number of operations performed	152
Patients having more than one operation	12
Total patients with satisfactory result (all techniques)	122 (95.31%)

TABLE III. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. GYNECOLOGIC SERVICE. POSTOPERATIVE TREATMENT

	EARLY	LATE
Warren technique	18	15
Layer method	45	11
Layer method with rectal sutures	32	7
Total	95	33

TABLE IV. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. GYNECOLOGIC SERVICE. TECHNIQUE USED ON PRIMARY ATTEMPT AT REPAIR

	TOTAL	SUCCESS	PARTIAL SUCCESS (PATIENT SATISFIED)	FAILURE
Warren technique	33	30	1 (93.93%)	2
Layer method	56	45	4 (87.5 %)	7
Layer method with rectal sutures	39	34	2 (92.3 %)	3

In the gynecologic service where the Warren or flap technic was used, one patient died of pulmonary embolus; three patients required resuture operations, all successful; one patient otherwise successful, developed a fistula. There were two failures, one having an infection of the wound and hemorrhage, and one a failure of union of sphincter fibers.

Where the layer method was employed, two patients required resuture operations, both successful; one patient had a fecal impaction on the twenty-third postoperative day with rupture of the sphincter, but was ultimately a success after healing by secondary intention; two cases were successful after a second attempt with rectal sutures; one a success after a second attempt by the layer method. One case

TABLE V. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. OBSTETRIC SERVICE (1923-1938)

Total deliveries		9,741
Total episiotomies performed		4,874
Episiotomy, median	4,580	
Mesiolateral	281	
Lateral	13	
Total number of complete lacerations		124 (1.27%)
Total number of repair operations	129	
Results: Satisfactory	96.0%	
Partially satisfactory (patient satisfied)	2.4%	
Failures	1.6%	
Lacerations, extension of episiotomy wound		124
Sphincter tears only	54	
Rectal tears	67	
Unspecified	3	

was a failure by the layer technic, again by the Warren method, and at the third attempt by rectal sutures was successful; one patient had a partial success after a second operation, and one a failure with no further attempt.

Where the layer method with rectal sutures was used there were three failures. One patient had eight attempts with a complete failure. She had been operated upon in several hospitals and finally came to us and was repeatedly operated upon by members of our staff; altogether she had two layer operations, two Warren, again two layer, one rectal suture, and one invagination of the rectum with mattress sutures which were all failures. There was practically no sphincter muscle left and the wound was in such a distressing condition that the patient seriously threatened suicide, having already made an attempt, so I did a Sistrunk colostomy operation and she is perfectly happy today, entirely relieved of her distress.

I agree with Dr. Phaneuf's emphasis on the importance of using fine sutures rather than heavy ones. Personally I prefer a silver wire suture to reinforce the sphincter muscle and use the Warren technic by preference.

DR. LILIAN K. P. FARRAR, NEW YORK, N. Y.—I was led some years ago to try to develop a technic because of unsatisfactory results that I had had in repair of third-degree lacerations. I visited various New York clinics to see how my neighbors handled the problem. I remember one surgeon putting numerous stitches in the rectum. I thought then I probably had not sutured the rectum sufficiently but as the count rose, 20, 30, 40, 50, and 54 stitches in the rectum, I decided that technic was not for me.

I then became interested in the "Warren Apron," described by J. Collins Warren, a Fellow of this Society and Professor of Anatomy and Surgery in Harvard Medical School. I decided to try it in lacerations of the sphincter ani with a laceration extending high up the rectum. Although I have not had the number of cases to repair that Dr. Phaneuf reports, I have never had a failure.

Twice I have had to put in extra sutures, the first time because the patient jumped as I removed a wire and once when an intern placed the legs of the patient in stirrups and the sutures on one side cut out. Both cases, however, healed perfectly. I keep a finger in the rectum while placing catgut and wire sutures and then after a change of gloves I tie the sutures.

I do not believe wire sutures are absolutely necessary. Best of Nebraska and Miller and Brown of Ann Arbor report good results by this technic and they use catgut only. Wire sutures are, however, the tradition of the Woman's Hospital, and as I have had satisfactory results with them I continue to use them. (For a full description and illustrations of the operation, see Surgery, Gynecology and Obstetrics, April, 1930, p. 741, and also Curtis, A. H.: Obstetrics and Gynecology, Vol. III, Philadelphia, 1933, W. B. Saunders Company, pp. 77-83.)

DR. FREDERICK C. HOLDEN, NEW YORK, N. Y.—A number of years ago Dr. Ralph Pomeroy called my attention to the fact that if a sphincter ani was thor-

oughly and carefully dilated just before delivery, there was much less likelihood of subsequent injury to the sphincter by an extension of a perineal laceration or of a median episiotomy.

Where an operative procedure is indicated, I prefer the Warren operation which I do without the silver wire sutures.

DR. G. D. ROYSTON, ST. LOUIS, MO.—There are two things we have found of special value: first, that the intestine should be kept empty after operation until there has been time for satisfactory repair; and second, that defecation should be produced without trauma, from enemas and from unnecessary efforts at cleansing the repair.

Some years ago, I reported from the Washington University Clinic some 68 repairs of complete perineal laceration on 62 different patients. These 68 operations were performed by 13 or 14 men, including house surgeons and junior assistants. This comparative study showed that the best results were obtained in patients who were given liquid diet, without milk for two days prior to operation, and evacuated with castor oil and enemas on each of these two days.

Fine catgut, preferably No. 1 or smaller, in continuous suture gave better results than interrupted sutures, coarser catgut, or nonabsorbable material. The repaired wound was left strictly untouched by pitcher douches or other cleansing efforts along the line of repair. After operation, opiates were freely given. The postoperative diet consisted of liquids without milk or fruit juices until signs or symptoms of autointoxication appeared, when mineral oil, 1 ounce three times daily, was given for two days, followed by a bottle of citrate of magnesia, which usually produced a soft stool.

This method gave on hospital discharge only 4 failures to obtain primary union among 31 cases, as compared with 8 failures among 26 given enemas and 4 failures among 10 with spontaneous defecation. The result was unknown in one. The first defecation varied from one to twenty-three days after operation, most patients being carried from eleven to fifteen days without defecation following the repair. Both methods of operation were used, though we prefer the flap method.

DR. JOSEPH L. BAER, CHICAGO, ILL.—There has been no distinction made in the discussion nor in the original paper of the essential difference between the repair of a fresh obstetric injury and an old gynecologic third degree tear. In our experience we have no recollection nor record of a fresh repair failing to heal. It is with the old repairs that occasional difficulty arises.

Dr. Norman Miller reported a procedure used routinely in order to place the anteriorly united repair at rest. It is a subcutaneous posterior division of the sphincter, at the end of an operation being done to unite an old anterior separation. He has been most pleased with this procedure and finds that the posterior incision reunites spontaneously. I have done this several times, though with the fear that I might produce a posterior hematoma in the field, but healing was uneventful.

DR. PHANEUF (closing).—Dr. Farrar's technic of the flap method differs entirely from the one which we have used, but she has shown that equally good results could be obtained by it.

Dr. Holden's recommendation of the dilatation of the sphincter before performing an incision in the perineum at the time of delivery is logical and should be extremely helpful as a prophylactic measure in the prevention of complete tears.

I do not see the necessity of tying up the bowels for as long a period of time as Dr. Royston has advised.

(The remaining papers read at the meeting of the American Gynecological Society will appear in the December issue, namely, those of Caldwell, Schwarz, Bartholomew, and Montgomery.)

Correspondence

The Dosage of the Estrogens

To the Editor:

In the editorial on "The Dosage of the Estrogens" which appeared in the September issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, a passage in the first paragraph (last line) as well as in the third paragraph gives the impression that the terms "estradiol" and "theelol" refer to the same substance. The care with which these editorials are read is attested by the fact that we promptly received a number of inquiries as to whether it was really true that theelol was the same as estradiol.

I would greatly appreciate it if you would publish a statement making it clear that these two substances are distinct.

(Signed) MAX GILBERT, M.D.,
Medical Research Division, Schering Corporation.

The above letter brought the following reply from Dr. Robert T. Frank, the writer of the editorial referred to:

To the Editor:

Our attention has been called to an unclearness in the nomenclature of estrogens mentioned in the editorial in our September issue.

"Estradiol" corresponds to the terminology of dihydrotheelin and not of theelol which, according to the same terminology, corresponds to estriol.

(Signed) ROBERT T. FRANK, M.D.

To the Editor:

We would like to ask for your help in the matter of procuring fresh tissue specimens of hydatidiform mole and chorionepithelioma. In this laboratory we have been studying living cells of the early placenta in tissue culture and, therefore, have been anxious to compare malignant with nonmalignant cells derived from trophoblast. We are also very much interested in the production of prolactin by the cells of the placenta when they are maintained for long periods of time in continuous culture. One of the great difficulties in pursuing work of this sort with human material lies in the fact that it is difficult to get fresh specimens at fairly frequent intervals.

We would greatly appreciate any efforts on your part in helping us to get specimens of hydatidiform mole and chorionepithelioma. It is important that the specimens be collected under aseptic conditions and that they be placed in a sterile tightly stoppered bottle without the addition of any solution such as salt, and shipped to us by air mail, special delivery, and that we be notified by telegram "collect" that the specimen is being sent. A note on some of our work appeared in *Science* recently (*Science*, September 30, 1938).

GEORGE O. GEY, M.D.

The Johns Hopkins Hospital,
Baltimore, Md.